“STUDY OF CHANGES IN SERUM LEVELS OF CREATINE KINASE AND LIVER ENZYMES IN ORGANOPHOSPHORUS POISONING AND IT’S PROGNOSTIC SIGNIFICANCE”

Dissertation submitted to

THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY

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for the award of the degree of

M.D. BRANCH – I

GENERAL MEDICINE

CHENGALPATTU MEDICAL COLLEGE

THE TAMILNADU DR.

CHENNAI M.G.R.MEDICAL UNIVERSITY, INDIA.

APRIL 2015.

CERTIFICATE

Certified that this dissertation entitled **"STUDY OF CHANGES IN SERUM LEVELS OF CREATINE KINASE AND LIVER ENZYMES IN ORGANOPHOSPHORUS POISONING AND IT'S PROGNOSTIC SIGNIFICANCE"**is a bonafide work done by **Dr.A.Senthil Kumaran,** post graduate student of the Department of General Medicine, Chengalpattu Medical College, Chengalpattu, during the academic year 2012-2015. This work has not previously formed the basis for the award of any degree.

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DECLARATION

I **Dr.A.Senthil kumaran**, solemnly declare that the dissertation titled, **"STUDY OF CHANGES IN SERUM LEVELS OF CREATINE KINASE AND LIVER ENZYMES IN ORGANOPHOSPHORUS POISONING AND IT'S PROGNOSTIC SIGNIFICANCE"** is a bonafide work done by me at Chengalpattu Medical College during 2011-2014 under the guidance and supervision of **Prof. Dr.KULOTHUNGAN,M.D.,** Professor, Department of General Medicine, Chengalpattu Medical College, Chengalpattu. The dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University, towards partial fulfillment of requirement for the award of **M.D. (General Medicine)**

Place: Chengalpattu **Dr.A.Senthil kumaran**

Date :

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CHENGALPATTU MEDICAL COLLEGE AND HOSPITAL,

CHENGALPATTU.

For granting me permission to utilize the resources of this institution for my study.

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I bow my head in respect before God Almighty

Date: **Signature of the Candidate**

Place: Chengalpattu **Name:Dr.A.Senthil Kumaran**

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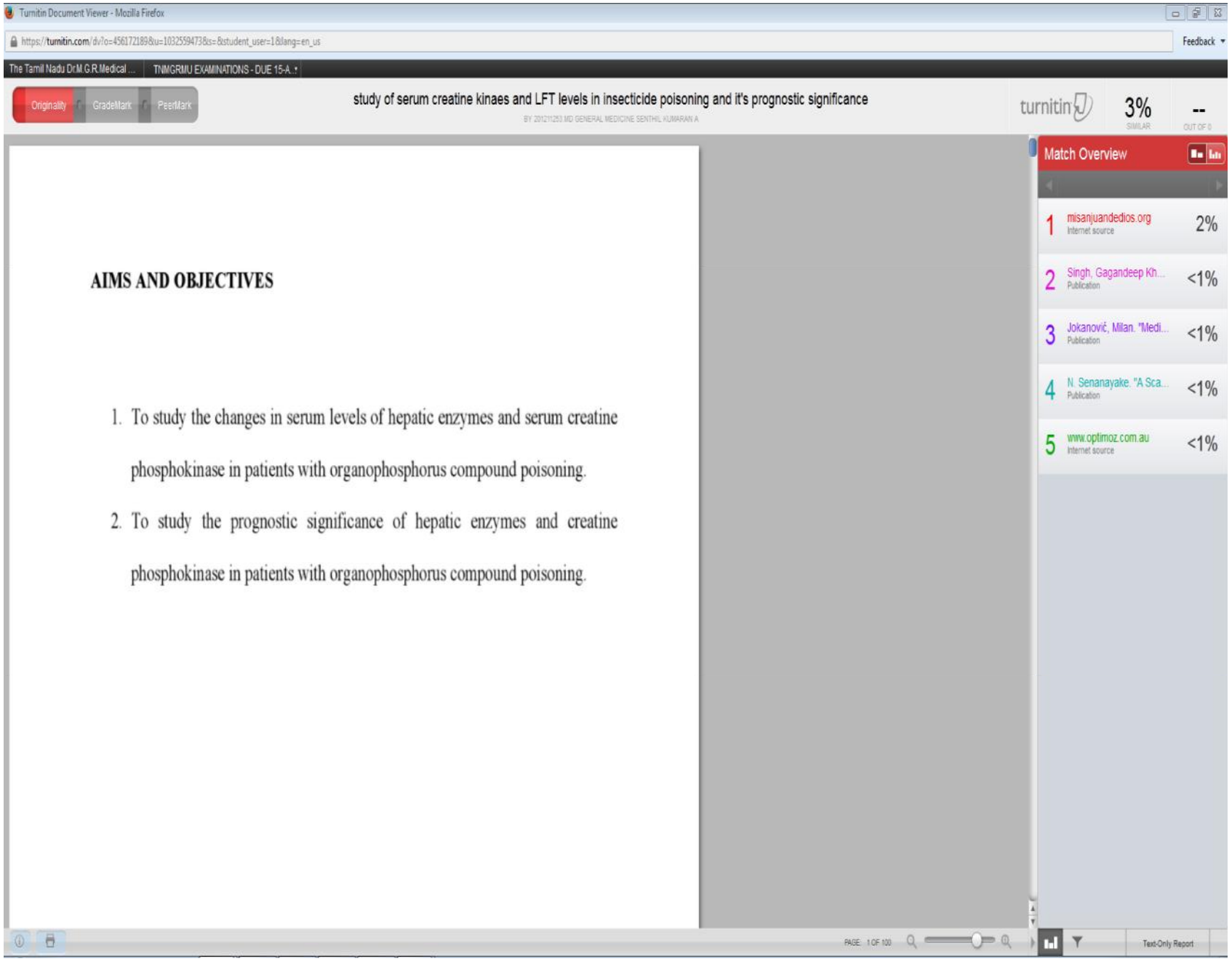
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1. To study the changes in serum levels of hepatic enzymes and serum creatine phosphokinase in patients with organophosphorus compound poisoning.
2. To study the prognostic significance of hepatic enzymes and creatine phosphokinase in patients with organophosphorus compound poisoning.
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LIST OF ABBREVIATIONS

Ach	**Acetylcholine**
Anti- ChE	**Anticholinesterase**
AOPP	**Acute organophosphorus poisoning**
AST	**Aspartate transaminase**
CPK	**Creatinine phospho Kinase**
CNS	**Central nervous system**
CT	**Concentration time**
CYP	**Cytochrome P**
DDT	**Dichlorodiethyltrichloroethane**
ECG	**Electrocardiogram**
ELISA	**Enzyme linked immunosorbent assay**
EPA	**Environmental protection agency**
GABA	**Gama amino butyric acid**
GDP	**Gross domestic product**
GI	**Gastrointestinal**
HI-6	**Asoxime**
ICU	**Intensive care unit**
IFCC	**International Federation of Clinical Chemistry**

IM	**Intramuscular**
IMS	**Intermediate syndrome**
IV	**Intravenous**
LD50	**Lethal Dose 50%**
LDH	**Lactate dehydrogenase**
LFT	**Liver function test**
LuH-6	**Obidoxime**
NCRB	**National crime records bureeau**
NMJ	**Neuromuscular junction**
NTE	**Neuropathy target esterase**
OP	**Organophosphorus**
OPIDN	**Organophosphate-induced delayed neuropathy**
PAM-2	**Pralidoxime**
PON1	**Paraoxonase 1**
POP	**Peradeniya organophosphorus scale**
PPE	**Personal protective equipment**
RBC	**Red blood cells**
RCT	**Randomised controlled trial**
RSI	**Rapid sequence intubation**

SGOT	**Serum glutamic oxaloacetic transaminase**
SGPT	**Serum glutamic pyruvate transaminase**
TEPP	**Tetraethyl pyrophosphate**
TMB-4	**Trimedoxime**
WHO	**World health organization**

CERTIFICATE

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Signature of the guide

Prof. R . Kulothungan,M.D.,

Department of medicine,

CMCH.

AIMS AND OBJECTIVES

1. To study the changes in serum levels of hepatic enzymes and serum creatine phosphokinase in patients with organophosphorus compound poisoning.
2. To study the prognostic significance of hepatic enzymes and creatine phosphokinase in patients with organophosphorus compound poisoning.

REVIEW OF LITERATURE

Dr. Kuntal Bhattacharyya[1], did a prospective study in 2011 in the Department of General Medicine, Government Medical College, Kolkotta, India, studied 63 patients of Organophosphorus poisoning to find out the level of Creatine kinase and its prognostic significance. The serum Creatine kinase level was estimated for 61 patients. Two patients (Initial CPK 1138 IU/L & 1086 IU/L) collapsed out of complications during the course of therapy on day 3 & day 5 respectively.

It was found that mortality was more in patients with high initial CPK level. Another 3 patients developed intermediate syndrome on day 3, had initial Creatine kinase level 1138 IU/L & concluded serum Creatine kinase can be an efficient biomarker in case of acute Organophosphorus poisoning.

S.B. Agarwal and V.K. Bhatnagar[2], in the year 2007 conducted a prospective study in acute OPC poisoning patients treated in the In-Patient Dept. of General Medicine, B.J.M.C.H, Ahmedabad. 121 patients were studied and found that the levels of serum LDH and Creatine kinase levels were markedly elevated

among poisoning cases indicating muscular impairment due to Organophosphorus toxicity. The Creatine kinase level was markedly increased among poison cases and there was high elevation in patients who collapsed.

A.Patel, V.Shivgotra & V.Bhatnagar[3], in the year 2008 conducted a prospective study in workers engaged in Organophosphorus insecticide production. About 161 workers were involved as subjects in the study. There was 40 subjects in control group, 50 subjects in maintenance group and 71 subjects in exposed group. The serum levels of SGOT & SGPT, was in the normal level in the controlled and in the subjects, who were exposed.

Antonio F. Hernández[4], in the year 2006 conducted a cohort study involving more than 100 intensive farmers. The renal and liver parameters like urea, creatinine, SGOT, SGPT and LDH was tested twice during the time for spraying. Cholinesterase suppression by more than 25% was used as criteria for estimating insecticide exposure. The results showed a correlation with increase in SGOT, SGPT and LDH levels.

Dilshad Khan, Mahwish Bhatti, Farooq Khan, Syed Naqvi, Karam A[5], Pathologists in Army Medical College, in 2008, conducted a prospective study on 109 patients and concluded that butryl cholinesterase level was significantly($P<0.001$) reduced in the farmers exposed to insecticide when compared to controls. Biochemical parameters like SGOT, SGPT, CKP,lactate dehydrogenase were markedly raised in the insecticide exposed agriculture workers as compared to control group. Total insecticide residues showed a highly significant correlation with SGOT, LDH, SGPT.

INTRODUCTION

Acute poisoning by Organophosphosphorous insecticide (OP) has reached epidemic proportions in most parts of the world, particularly in developing countries like India, where agriculture is the backbone. The toxicity of Organophosphosphorous poisoning and paucity of appropriate medical facilities accounts for a high fatality rate. Their ease of access and socio–cultural factors play important role in choice of OP as a self-poison and the incidence is higher among young economically active group with a common fatality ratio of 20%. Insecticide compounds cause many number of suicidal deaths in South and Central India[6].

Occupational, suicidal or homicidal exposure to OPs produces a characteristic, but treatable syndrome in humans. Thus, early recognition and timely intervention of toxicity from these compounds are of great importance, to critical care providers and patients.

Case reports[7] on clinical significance of liver enzymes and creatine kinase in acute organophosphorous compound ingestion has been reported now and then, but there are no large-scale studies with reference to clinical significance of liver enzymes and Creatine kinase. Hence an attempt will be made to study clinical significance of liver enzymes and Creatine kinase in OP poisoning.

HISTORY OF ORGANOPHOSPHORUS COMPOUNDS:

In this field the earliest scientists are J Loui Lssaigne and Philippe Clermonte (early in nineteen hundred century) [8]. Around 1932,chemist in germany by name Willy Lange and his student, Gerde Krueger, was first to describe the cholinergic CNS effects oforganophosphorus. The earliest organophosphorus compound, tetraethyl pyrophosphate (TEPP), was produced in middle of nineteenth century, but the compound not used till second world war, in which

nicotine a rare pesticide was replaced by tetraethyl pyrophosphate. The toxicity of organophosphorus was utilized in the secondworld war by Germans with the production of the nerve gas agents[9].

After Second World War, US companies got information from Schrader's laboratories, and started producing organophosphorus compounds in huge quantities. The first marketed compound was Parathion, followed by Malathion and Azinphosmethyl. These insecticides became famous when organochlorine insecticides like DDT, Dieldrin, and Heptachlor were banned in the middle of twentieth century.

The mechanism of action of organophosphorus compound was understood after the massive Jamaican ginger palsy accident which took place in the year 1930.[10]

STRUCTURE OF ORGANOPHOSPHATES[11]:

Organophosphorus are heterogenous compounds sharing similar chemical properties. Organophosphorus has a P atom in the central group with a double bond to O2or S (P=S) either, two side chains of organic (R1and R2), and an

side chain of additional that will act as leaving group (X). The individual organophosphorus is specific for its leaving group which can be a CN, thio-CNate, halide, phenoxy phosphate, thio-phenoxy, or carboxyl group. The R1and R2 can be aryl/alkyl groups and, in many of the common insecticides, are either two ethyl or two methyl esters that form the diethyl (diethoxy) or dimethyl (dimethoxy) OPC respectively.

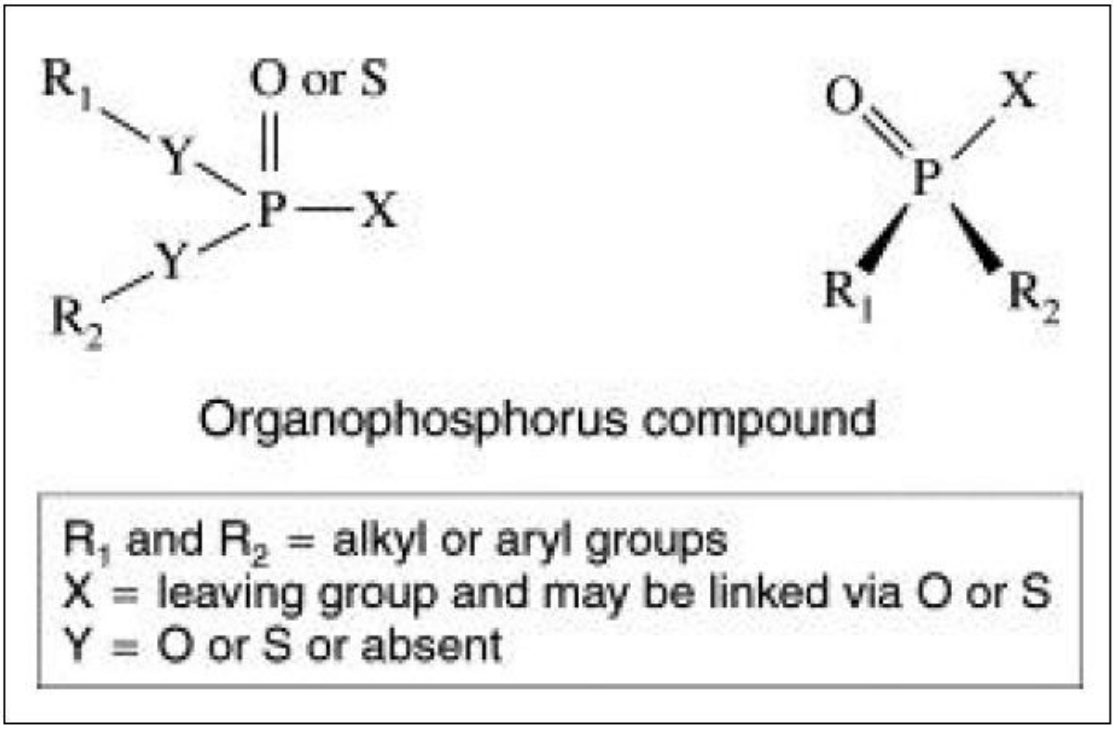


Fig 1: Structure of organophosphates

Chemical Classification of Representative Organophosphorus:

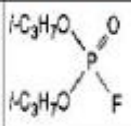
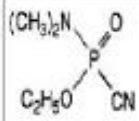
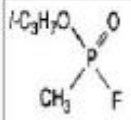
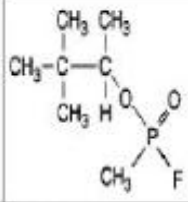
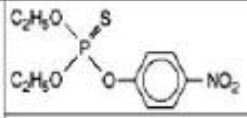
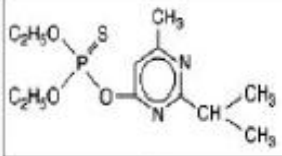
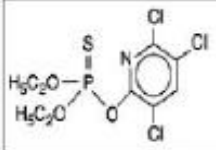
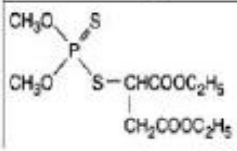
Compounds

Group A, X = halogen, cyanide, or thiocyanate leaving group;

Group B, X =alkylthio, arylthio, alkoxy, or aryloxy leaving group;

Group C, thionophosphorus orthio-thionophosphorus compounds;

Group D, pyrophosphates and similar compounds;group E, quaternary ammonium leaving group. R1can be an alkyl (phosphonates), alkoxy (phosphorates) or an alkylamino (phosphoramidates) group.

GROUP	STRUCTURAL FORMULA	COMMON, CHEMICAL, AND OTHER NAMES	COMMENTS
A		DFP; Isoflurophate; diisopropyl fluorophosphate	Potent, irreversible inactivator
		Tabun	Extremely toxic "nerve gas"
		Ethyl *N*-dimethylphosphoramidocyanidate	
		Sarin (GB)	Extremely toxic "nerve gas"
		Isopropyl methylphosphonofluoridate	
		Soman (GD)	Extremely toxic "nerve gas"
		Pinacolyl methylphosphonofluoridate	
C		Parathion	Employed as agricultural insecticide, resulting in nu cases of accidental poisoning; phased out of agricu 2003.
		O,O-Diethyl *O*-(4-nitrophenyl)-phosphorothioate	
		Diazinon, Dimpylate	Insecticide in wide use for gardening and agricultur banned for indoor use and being phased out of all in 2005
		O,O-Diethyl *O*-(2-isopropyl-6-methyl-4-pyrimidinyl) phosphorothioate	
		Chlorpyrifos	Insecticide with restricted use in consumer product to nonresidential settings
		O,O-Diethyl *O*-(3,5,6-trichloro-2-pyridyl) phosphorothioate	
		Malathion	Widely employed insecticide of greater safety than other agents because of rapid detoxification by hig organisms
		O,O-Dimethyl *S*-(1,2-dicarbethoxyethyl) phosphorodithioate	

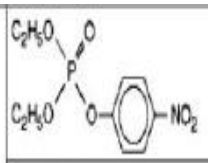
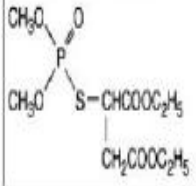
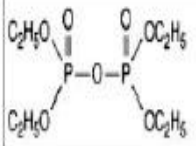
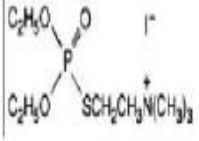
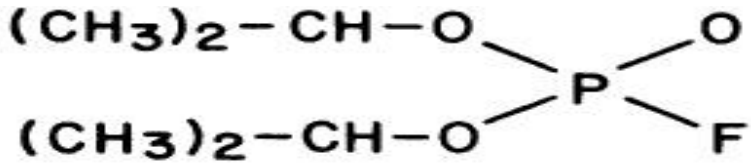
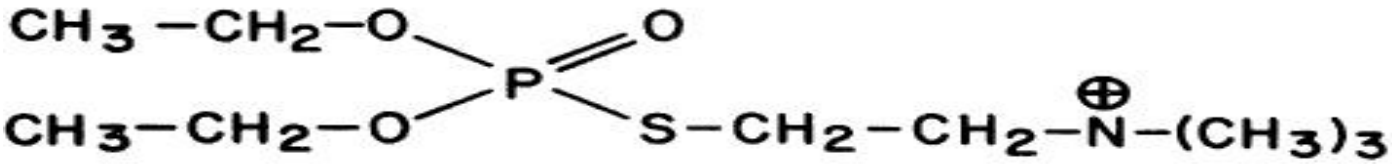
B		Paraoxon (MINTACOL), E 600	Active metabolite of parathion
		O,O-Diethyl *O*-(4-nitrophenyl)-phosphate	
		Malaoxon	Active metabolite of malathion
		O,O-Dimethyl *S*-(1,2-dicarboxyethyl)-phosphorothioate	
D		TEPP	Early insecticide
		Tetraethyl pyrophosphate	
E		Echothiophate (PHOSPHOLINE IODIDE), MI-217	Extremely potent choline derivative; employed in treatment of glaucoma; relatively stable in aqueous solution
		Diethoxyphosphinylthiocholine iodide	

Table 1. Classification of OP compounds



DIISOPROPYL FLUOROPHOSPHATE (DFP)

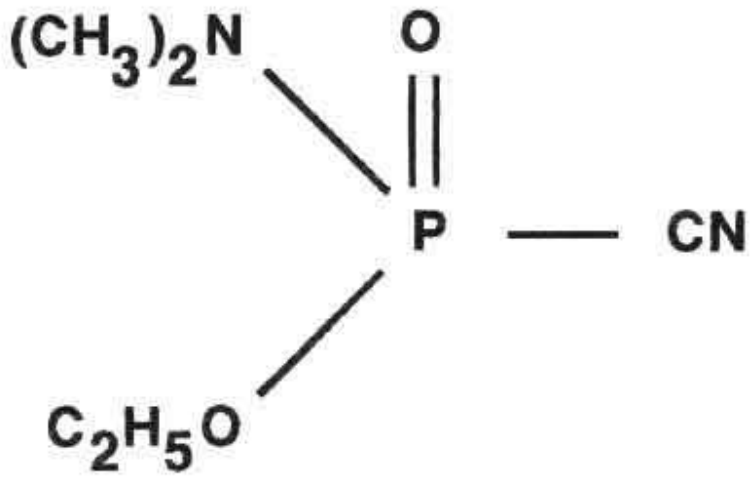


ECHOTHIOPHATE (PHOSPHOLINE)

structural formula of di-isopropyl fluorophosphate.

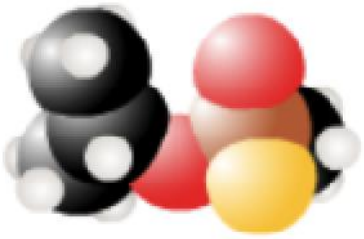
This compound belongs to group A and it is a potent irreversible in activator of acetylcholinesteras.

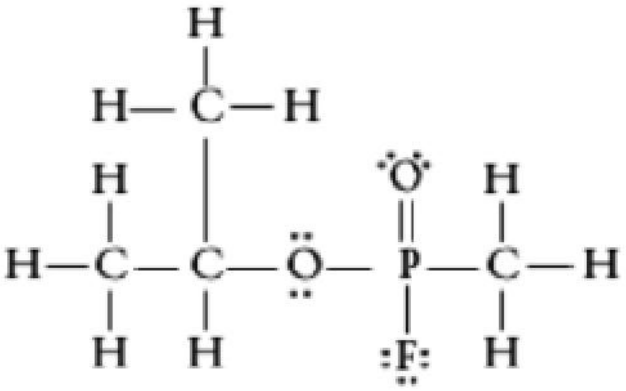
TABUN / GA NERVE AGENT
Ethyl N-dimethylphosphoamidocyanidate



Structural formula of tabun which belongs to group A Organophosphorus compound and it is a extremely toxic nerve gas agent.

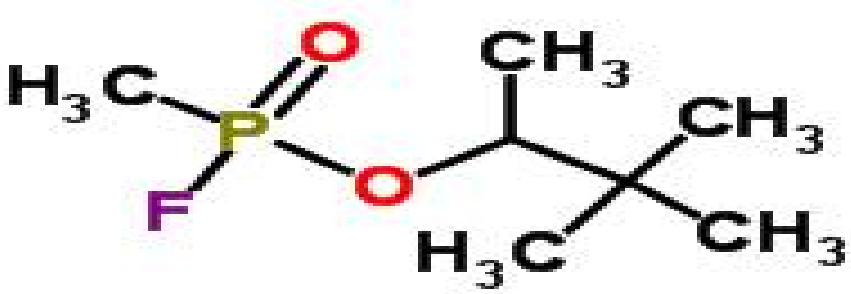
Structural formula of sarin.





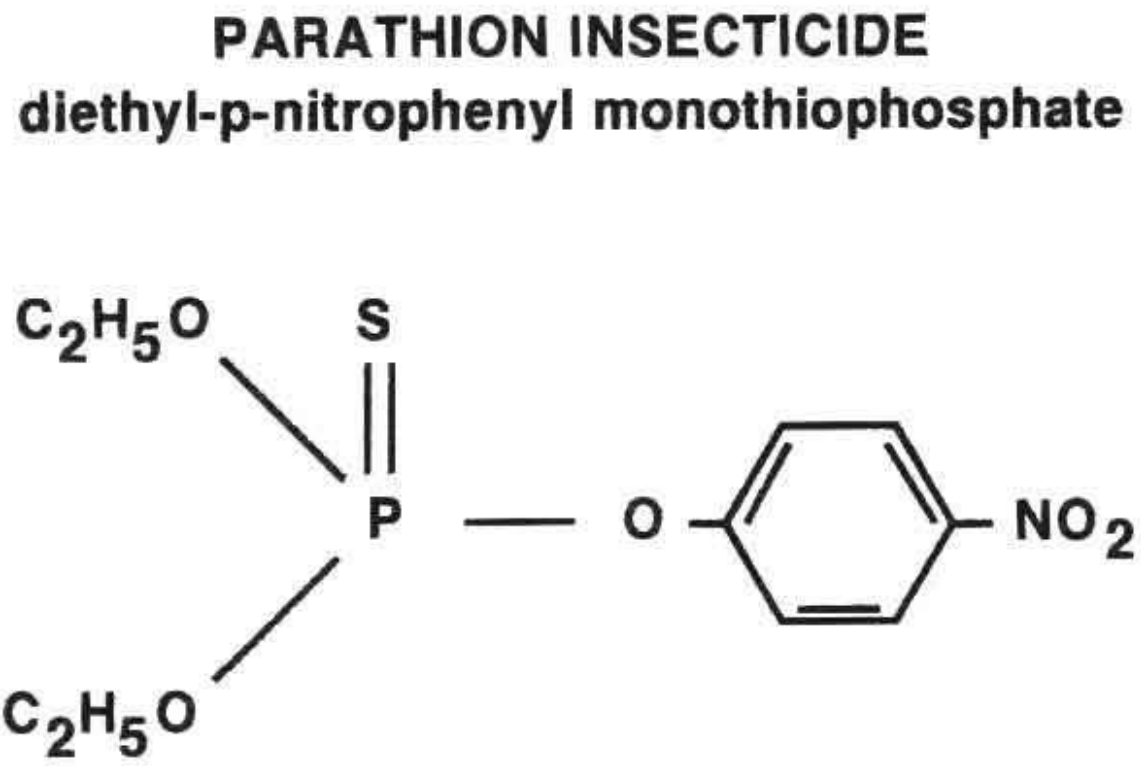
This compound belongs to group A of organophosphorus compound and it is a also a extremely toxic nerve gas agent. It’s chemical name is isopropyl methyl phosphonofluridate.

Structural formula of soman.



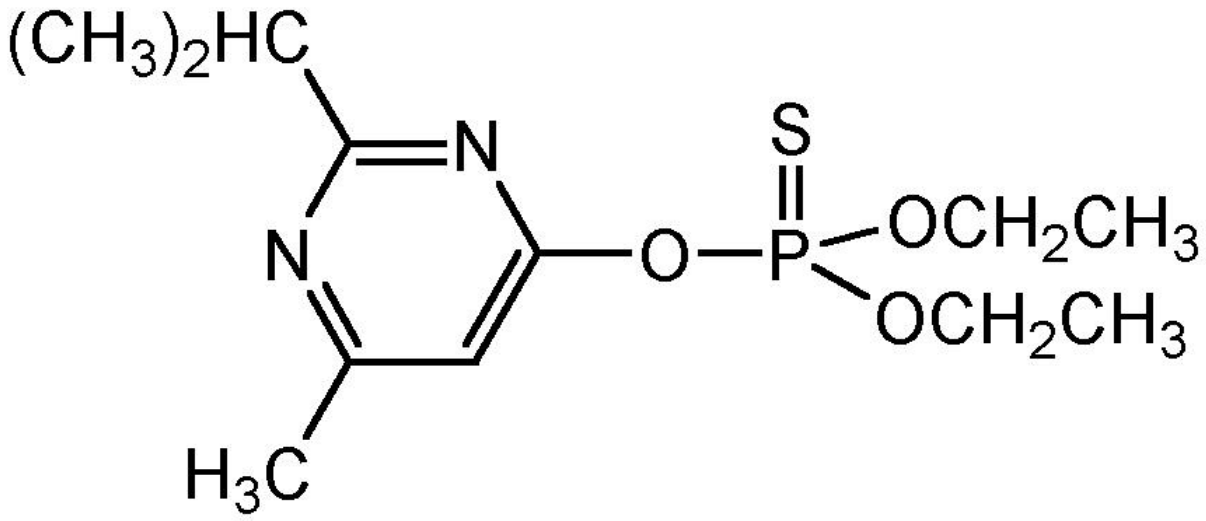
This compound also belongs to group A of organophosphorus compound. It also a extremely toxic nerve gas agent. It's chemical name is pinacolyl methyl phosphonofluridate.

Structural formula of parathion



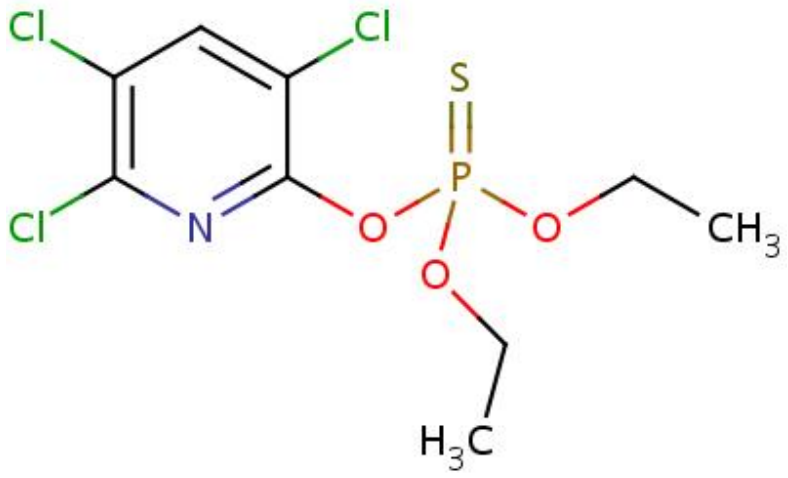
This compound belongs to group C of organophosphorus compound. Commonly used agricultural pesticide and it is one of common cause of accidental poisoning.

Structural formula of diazinon



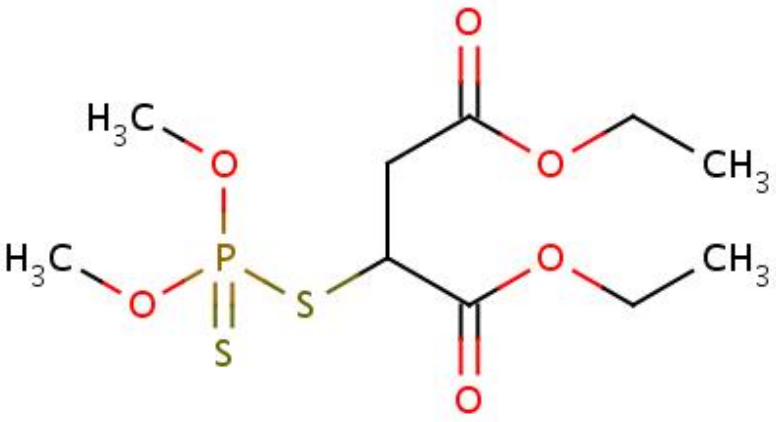
This compound belongs to group C of organophosphorus compound. It is commonly used for agricultural and gardening purpose. It is banned for indoor use.

Structural formula of chlorpyrifos



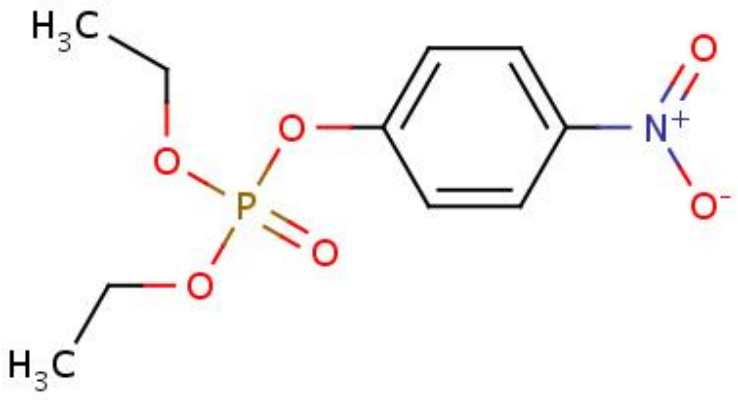
This compound belongs to group C of organophosphorus compound and it one of the commonly used agricultural pesticides.

Structural formula of malathion



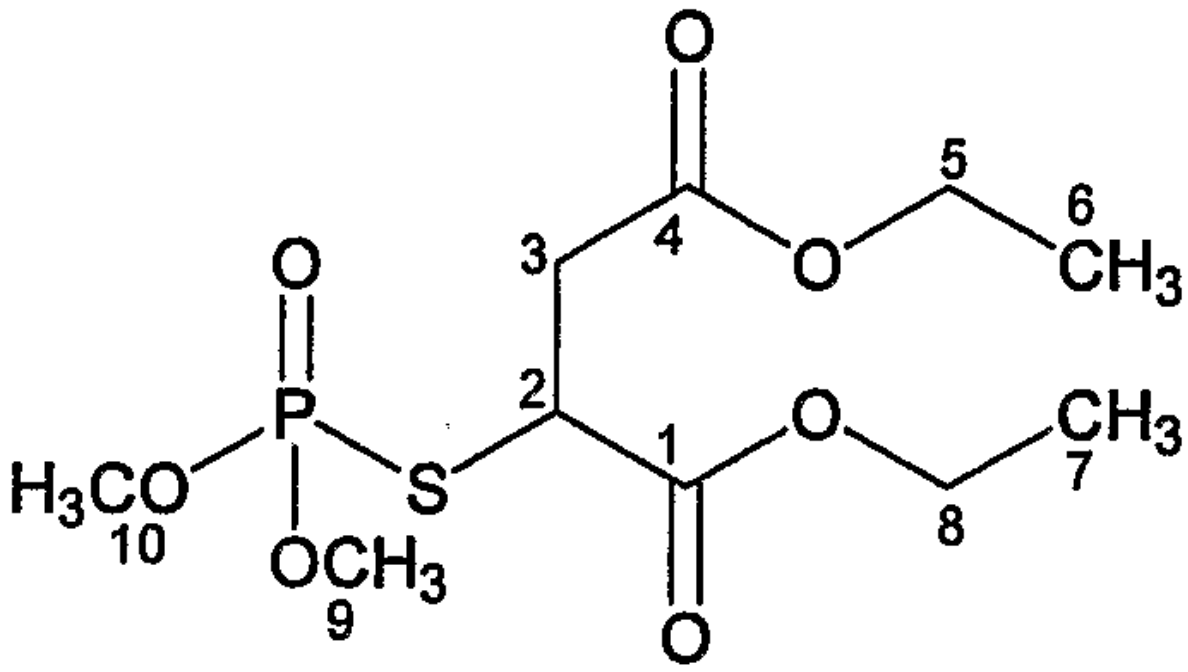
Malathion belongs to group C of organophosphorus compound and it is widely used insecticide because of it's property of rapid detoxified by higher organism and superior safety when compared to parathion.

Structural formula of paraoxon



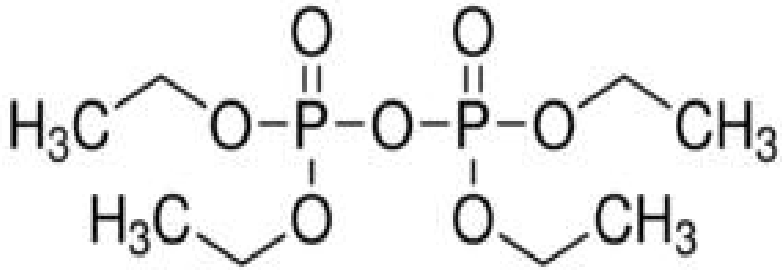
This compound belongs group B of organophosphorus compound. It is a active metabolite of parathion. It's chemical name is o,o-diethyl,o-4-nitrophenl-phosphate.

Structural formula of mlaoxon



Malaoxon is a active metabolite of malathion and it belongs to group B of organophosphorus compound. It chemical name is O,O dimethyl S-(1,2-dicarboyethyl)-phosphorothioate.

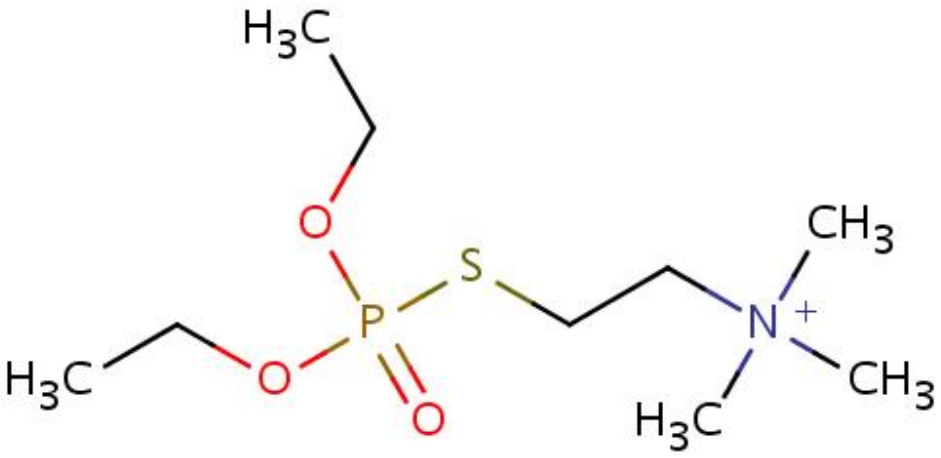
Structural formula of TETRA ETHYL PYROPHOSPHATE



TEPP

This is one of earliest pesticide. And it belongs to group D of organophosphorus compound.

Structural formula of echothiophate.



This compound belongs to group E of organophosphorus compound. This is a potent choline derivative. It is commonly used in the treatment of glaucoma. It is highly stable in aqueous solution.

EPIDEMIOLOGY:

Global Status:

The serious human toxicity associated with organophosphorus compounds accounted for more than 80% of hospitalization[12] related to pesticide poisoning. In contrast to organo chlorine, organophosphorus was used because of their unstable nature, rapid hydrolysis and no long period accumulation in environment.

There is an increased number of poisoning due to its widespread use. In early 1970 EPA[13] conducted a survey which showed around 3000 hospitalization with insecticide poisoning in America with a case fatality rate of around 50% in Paediatrics and ten percent in adults. In 1980's study[13] given by US association of poison control centre showed incidence of 77000 of which the compound is organophosphate in 33000 cases.

A survey conducted[13] in Bangaladesh showed 14% of death of females in the age group of 10 to 50 is suicidal poisoning of which majority is due to insecticide. The situation is worse in Sri Lanka in which insecticide poisoning is the most commonest cause of death in 6 districts.

The WHO data shows around 9 lakhs people[14] die annually due self harm of which more than 60% of death is due to insecticide poisoning and it is greater than self hanging and other modes of self harm.

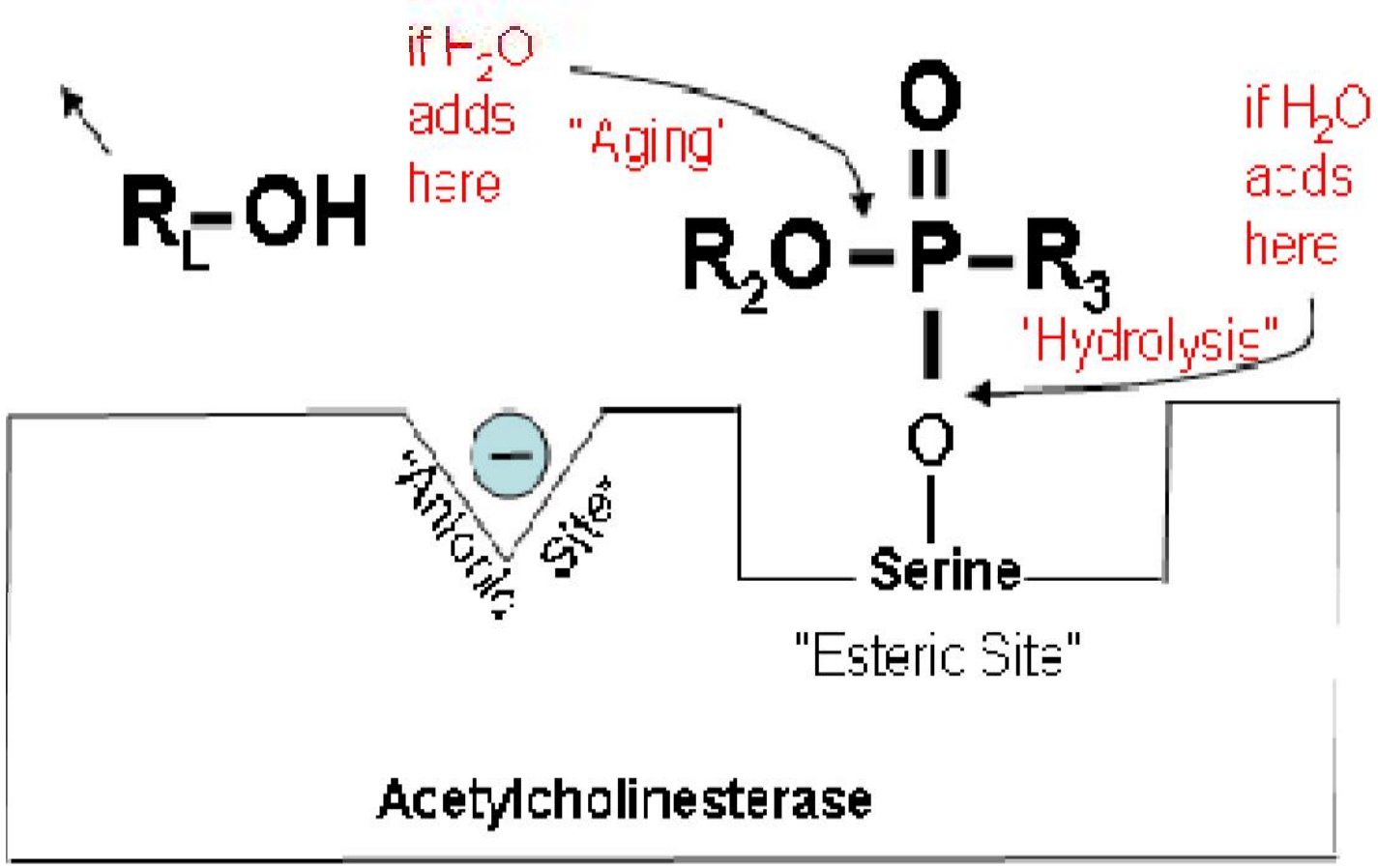
National status:

India is an agricultural country and by far India is highly dependent on agriculture for its GDP. Insecticide poisoning by far is very common in India due to cheap and easily availability. Furthermore, easy accessibility to children and lack of awareness makes insecticide poisoning common in India. Annually more than 126000 cases have calculated to occur in the year 2007 by Gunell et al[15].

PATHOPHYSIOLOGY OF TOXICITY[16]:

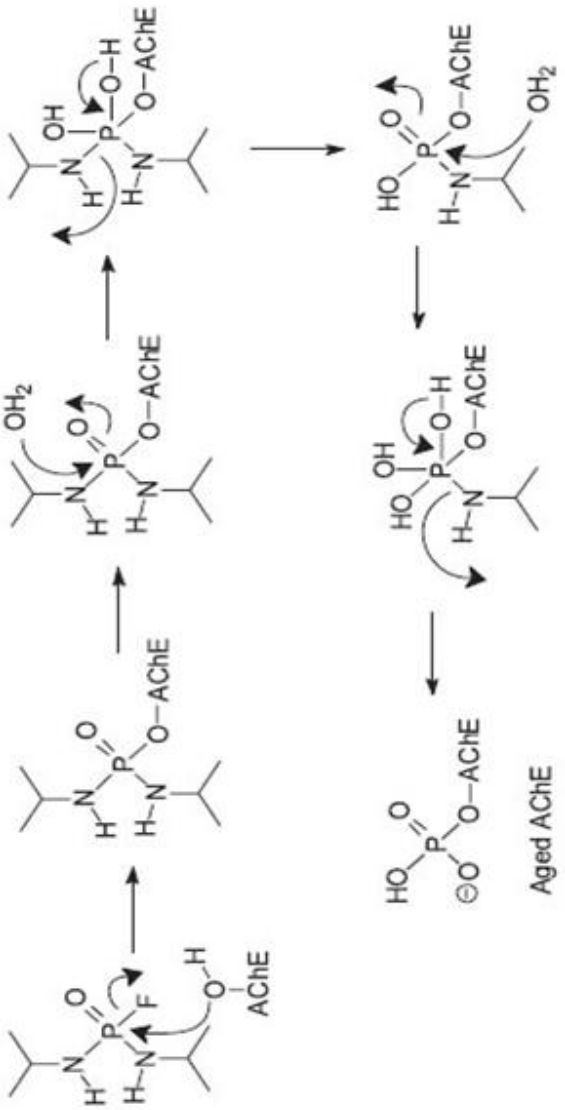
Mode of action of organophosphates is by binding to serine active site of Acetylcholinesterase. Due to inhibition of Acetylcholinesterase, acetylcholine begin to accumulate at nerve endings and their by paralyzing central and peripheral nicotic and muscuranic receptors. In normal condition acetyl cholinesterase hydrolyses acetyl choline to choline which is used for re-synthesis. When Acetylcholinesterase is blocked in case of poisoning acetylcholoine begins to accumulate which initially causes excitation followed by depolarization blockade at the post synaptic level.

Acetylcholinesterase exists in three forms true cholinesterase found in nervous tissue and it important for physiological conduction but it is difficult to estimate. Pseudocholinesterase is found in serum and liver and it is easily to calculate and it is responsible for metabolism of xeno-biotics. Erythrocyte acetyl cholinesterase is similar to true or neuronal cholinesterase and it is difficult to calculate.


if H2O adds here
"Aging"
if H2O adds here
'Hydrolysis"
RL–OH
R2O–P–R3
O
O
Serine
"Anionic Site"
"Esteric Site"
Acetylcholinesterase

Acetylcholinesterase is a protein structure which contains a serine binding site and a catalytic site. Organophosphorus compounds form a reversible Michelis-Menten complex by binding to serine enzymatic site and cause rapid phosphorylation of the serine residue. Following that, the leaving group is ejected from the organophosphorus compound. During this process organophosphorus compounds binds to the enzyme on the pit and produces a conformatory change in the enzyme and thereby preventing the binding for acetylcholine to the enzyme and preventing enzymatic activity.

The organophosphorus bound enzyme will undergo 2 forms of reaction. First one is aging process or irreversible in activation by breakage of one of the R groups and this largely dependent on the nature of organophosphorus compound. Another reaction is reactivation of enzyme by the process of hydrolysis of the bond between the serine and organophosphorus compound. The R group attached to the organophosphorus compound is largely responsible for the enzyme to undergo reactivation or irreversible inactivation by aging process.



Mechanism of aging of acetylcholinesterase.

Organophosphorus compounds with smaller side chains undergo faster inactivation by aging process when compared to compounds with branching side chains. For examples dimethyl orgophosphates compound undergo faster inactivation when compared to diethyl organophosphorus compounds. Once the enzyme is aged it cannot be reactivated by either in vivo hydrolysis or by oxime treatment.

When the organophosphorus compound is consumed formation of axon peaks which follows decline in the serum. Even after the organophosphorus concentration in the serum decreases, Acetylcholinesterase inhibition continue to increase by the process of covalent binding.

Even a minimal amount of Acetylcholinesterase is enough for the normal functioning. Once this threshold is crossed even on removal the organophosphorus compound will act to restore the enzyme function. In case of dimethyl organophosphorus compounds enzymatic restoration occurs fast due to smaller side chain and it is delayed in case of dimethoate due to branched side chain. The reactivation of acetylcholinesterase with oxime is by the formation of transient complex with phosphorylated enzymes.

Once this formation of complex undergoes saturation kinetics further addition of oxime shows no effect on further reactivation.

The oximes remove the organophosphorus from the Acetylcholinesterase molecule and causes reactivation of the Acetylcholinesterase. Poisoning with highly lipophilic agents like fenthion, develop toxicity even after oxime therapy due to prolonged elimination.

Anticholinesterase compound produces its toxic effects by stimulation of muscarinic receptors followed by depression of autonomic ganglia and skeletal muscles and depression or stimulation of muscuranic receptors in the central nervous system.

Compounds belonging to quarternary amino groups do not penetrate cell membrane readily. Hence compounds belonging to this group are poorly absorbed from gastrointestinal tract or through the skin and does not penetrate blood brain barrier.

These compounds preferentially act at neuromuscular junction of skeletal muscles whenever highly lipophillic compounds penetrate skin and gastro

intestinal tract easily and they affect the central nervous system by readily crossing the blood brain barrier.

PHARMACOKINETICS:

Insecticides commonly used are generally dispersed as aerosols and are adsorbed as inert, fine particles. Insectides are absorbed directly via skin and mucous membrane, or by inhalation to lungs, or by ingestion to gastro-intestinal tract.

Most organophosphorus compounds are excreted through urine after hydrolsis. Plasma and hepatic enzymes like esterases hydrolyze OPC’s to the phosphoric and phosphonic acid derivatives.

Also, the CYPs convert the inactive phosphorothioates containing a phosphorus-sulfur (thiono) bond to phosphorates with a phosphorusoxygen bond, resulting in their activation.

The organophosphorus anti-ChE agents are hydrolyzed by two types of enzymes: a) the carboxylesterases and b) the paraoxonases (A-esterases), which are found in the plasma and hepato-biliary system. They tend to scavenge a large number of organophosphorus compounds by cleaving the phosphoester, anhydride, PF, or PCN bonds. The paraoxonases are low-molecular-weight enzymes, requiring Ca2+ for catalysis. Isoenzymes control low density lipoprotein oxidation, thus providing a protective effect in atherosclerosis. Organophosphate substrate specificity and susceptibility to atherosclerosis are found to have genetic susceptibility.

Plasma and hepatic carboxylesterases (aliesterases) and plasma butyrylcholinesterase are inhibited irreversibly by organophosphorus compounds; These are the main scavenging enzymes of AChE in the nervous system. The carboxylesterases also catalyze hydrolysis of malathion and other carboxyl-ester linkage containing OPCs, rendering them less active or inactive. Since carboxylesterases are inhibited by organophosphates, toxicity from exposure to two organophosphorus insecticides can be synergistic.

Absorption:

The percentage of absorption depends on

a) Duration of time in contact with mucous membrane and skin.
b) Liphophilic nature of the insecticide compound consumed.
c) Volatile nature of the compound.
d) Nature of the area which comes in contact for example skin of axilla, head and mucous membrane absorb more insecticide when compared skin of hands and palms.
e) Type of dress worn during poisoning and it's permeability,
f) Percentage of body uncovered and exposed to pesticide at the time of poisoning.;
g) Molecular weight of the compound consumed. (Less molecular weight are absorbed more quickly)

Distribution and Storage:

Organophosphorus compounds are widely stored in fat tissues and moreover they are lipophilic which responsible for delayed toxicity even after initial apparent

recovery. They are largely stored in salivary glands, liver and kidney. As they are lipophilic the easily cross the blood brain barrier and affect the central nervous system rapidly.

Elimination:

Elimination is mainly through urine and faeces. Small amount is excreted through expired air. Dichlorvos which are not liphophilic is excreted rapidly whereas chlorpyrifos which are liphophilic is stored in fat for longer period and are eliminated for days.

TOXICICOLOGY:

Toxic effects of the agent largely depend on the type of compound consumed, amount of compound consumed, route and duration of contact with the offending agent.

WHO[17] classified the organophosphorus compound as extremely hazardous, moderately hazardous and slightly hazardous on the basis of lethal dose of 20-200mg/kg, 200-2000mg/kg and >2000mg/kg respectively.

Hence the lethal dose can be as low as few mgs to as high as 50 gms for hidghly toxic and least toxic compounds respectively. For nerve agents lethal dose may be as low as 1 mg for sarin.

CLINICAL MANIFESTATIONS OF ORGANOPHOSPHORUS

POISONING:

Acute Intoxication

Signs and symptoms of insecticide compound depend on the amount of compound consumed, route of administration and nature of compound and duration of contact with the offending agent.

After exposure symptoms include constriction of pupils, ciliary paralysis, congestion of conjunctiva and painful eye. With systemic intoxication constriction pupils will not be evident due sympathetic stimulation due to hypotension.

Respiratory symptoms are due to rhinnorhea hypersecretion in the respiratory tract. Chest discomfort and wheezing are due to increased secretion in the bronchial airways. Gastro intestinal symptoms include nausea, vomiting, abdominal pain and diarrhea.

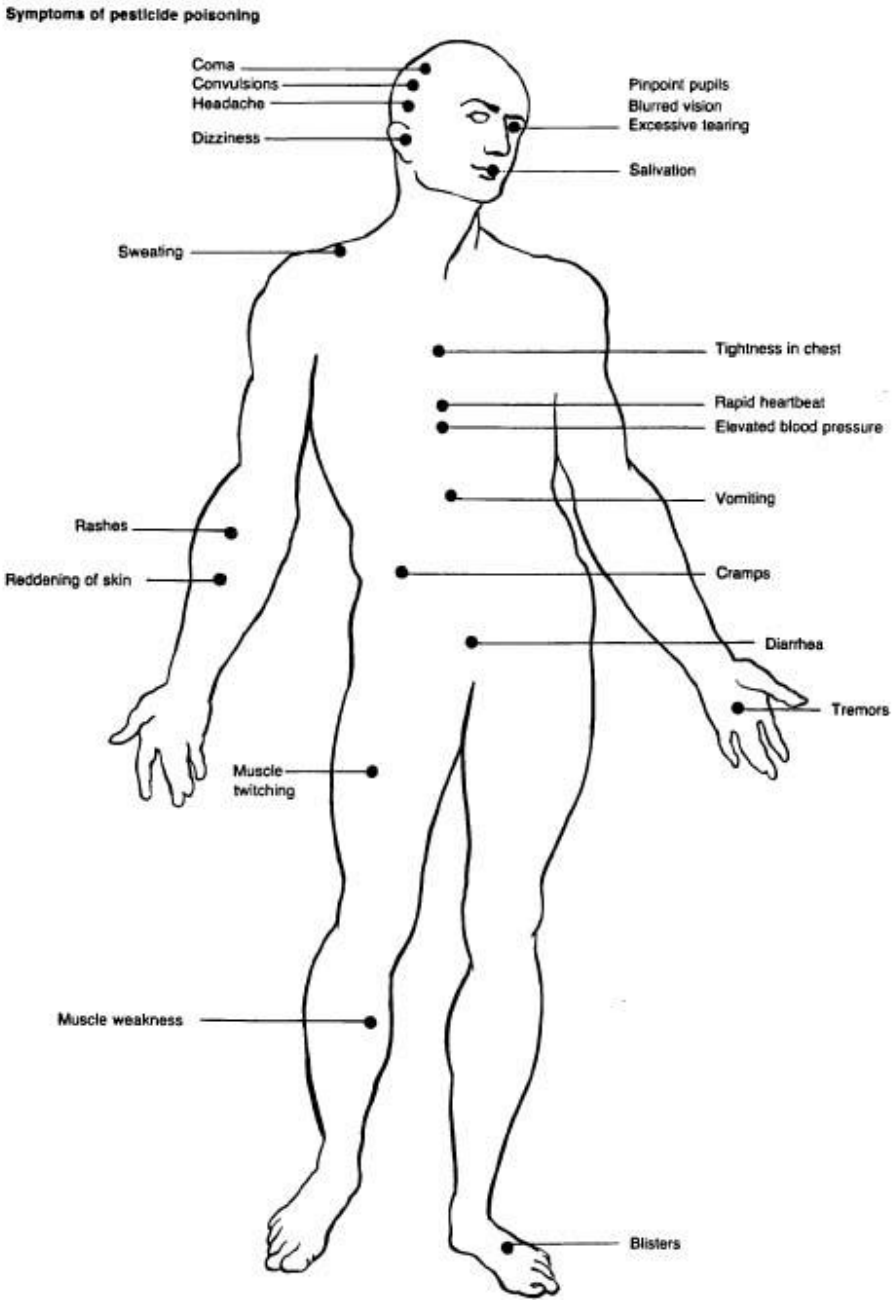
Severe toxicity manifest as involuntary defecation and urination, increased lacrimation, bradycardia and hypotension, severe muscle weakness and paralysis. CNS manifestation include confusion, ataxia, rapid breathing (Chynes-Stokes), generalized convulsion, coma, respiratory paresis and hypotension.

Death can occur from insecticide poisoning from as short as 5 minutes to 24 hours depending on the type of compound consumed, route of administration, amount of compound consumed and time delay in presentation.

Muscarinic	**Nicotinic**	**Central**
Increased salivation Increased lacrimation Increased urination Increased defecation Abdominal cramps Vomiting Miosis Respiratory difficulty Faecal and urinary incontinence	Hypertension Tachycardia Muscle weakness/paralysis Muscle fasciculation Pallor Mydriasis	Confusion Convulsions Psychosis Fatigue Respiratory depression Ataxia Dysarthria anxiety

Table 2 : symptoms of OP poisoning .

Cholinergic Toxidrome	
Muscarinic Symptoms	**Nicotinic Symptoms**
S – Salivation	**M** – Muscle cramps
L – Lacrimation	**T** – Tachycardia
U – Urination	**W** – Weakness
D – Defecation	**T** – Twitching
G – GI cramping	**F** - Fasciculations
E – Emesis	



Symptoms of organophosphorus poisoning.

INTERMEDIATE SYNDROME

In 1987, Senanayake[18] defined a condition which occurs on second to third day after cholinergic crisis and it is characterized by proximal muscle weakness, neck muscle weakness and respiratory failure.

The syndrome has been characterized by absent muscarinic symptoms but continued severe acetylcholinesterase inhibition as measured by cholinesterase activity, and there is no therapy other than supportive care. There is no definite etiology or treatment for intermediate syndrome. Treatment is mostly supportive therapy. But some authors recommend addition oximes for intermediate syndrome with no definite results.

TOXIC DELAYED POLYNEUROPATHY DUE TO OPC:

Organophosphorus compounds inhibit neuropathy target esterase which on loss causes demyelination of axons. This causes symptoms like paraesthesia, pain and distal muscle weakness which usually starts after 6 weeks of illness and may progress upto 6 months. There is no definite treatment for this condition and it is diagnosed by estimating lymphocyte NTE assay.

OTHER RELATED DISORDERS:

There are other delayed neuropsychological effects like fatigue, confusion, dementia and depression.

DIAGNOSIS:

Diagnosis is mainly clinical. History of exposure to a known OP compound must be elicited, wherever possible. Estimation of serum or RBC cholinesterase level is the investigation of choice and clinches the diagnosis of OPC poisoning. Electrodiagnostic tests may be helpful.

When RBC cholinesterase activity is reduced by more than 25 % of normal, clinical features tend to appear, and severity is more common when the levels go below 90% of normal.

Despite these facts, serial studies and randomized control trials have failed to document a strict relationship between the severity of clinical manifestations and prognosis.

LABORATORY FINDINGS

Poisoning is confirmed by demonstration of decreased erythrocyte or butyrylcholinesterase activity, which needs to be hemoglobin standardised. Standardized Erythrocyte acetylcholinesterase does not exhibit the same inter-individual variability. The erythrocyte membrane contains erythrocyte acetylcholinesterase. Thus, pre-intoxication enzyme activity levels are dependent on formation of new erythrocytes (hematopoiesis - a process that extends from 90 to 120 days).

Butyrylcholinesterase is a acute-phase reactant which normalizes in twenty to thirty days. Genetic variation can occurs in three percent of normal population, causing baseline decrease in butyrylcholinesterase activity level. Parenchymal liver disease, congestive heart failure, metastatic carcinoma, pregnancy, and several medications can give false negative values for butrylcholinesterase.

Peradeniya organophosphorus poisoning (POP) scale:

The Peradeniya Organophosphorous Poisoning (POP) Scale was a Scoring System introduced by Senanayake et al[18] in 1993.Common clinical manifestations of OP poisoning are assessed on a three-point scale varying from 0 to 2. A score of 0 to 3 is considered as mild poisoning, 4 to 7 as moderate poisoning and 8 to 11 as severe poisoning.

Parameters	Criteria	Score
Pupil size	≥2 mm	0
	<2 mm	1
	Pinpoint	2
Respiratory rate	<20/min	0
	≥20/min	1
	≥20/min with central cyanosis	2
Heart rate	>60/min	0
	41–60/min	1
	<40/min	2
Fasciculation	None	0
	Present, generalized/continuous	1
	Both generalized and continuous	2
Level of consciousness	Conscious and rationale	0
	Impaired response to verbal commands	1
	No response to verbal commands	2
Seizures	Absent	0
	Present	1

Note: 0–3, mild poisoning; 4–7, moderate poisoning; 8–11, severe poisoning

Table 3: peradeniya organophosphorus poisoning scale.

MANAGEMENT:

Initial management:

Attention to the airway is the initial management in the organophosphorus or carbamate poisoning. Oxygen and atropinization should be done in the management of hypoxic symptoms like cyanosis, rales, excessive oral secretions and bronchorrhea. Atropine should be given till there is no evidence of pulmonary fluid and the secretions have dried.

Respiratory failure during atropinisation should be managed by continuous suctioning, intubation and ventilation. During rapid sequence intubation (RSI) in the organophosphorus poisoned patient, the use of a depolarizing agents like succinyl choline, is not recommended since it may result in prolonged paralysis because it is metabolized through butyrylcholinesterase.

Organophosphorus poisoning causes vasodilation resulting in significant GI fluid losses. The management should be giving loading dose of 4 points NS so that we can maintain a normal volume. When atropine and fluids are not able to correct the hypotension vasopressors like phenylephrine is indicated.

In case of seizures benzodiazepine agents like diazepam, lorazepam or midazolam can be used.

Decontamination:

After initial stabilization decontamination should be done. Percutaneous absorption of pesticides continues to take place via skin and mucous membrane. Hence patient should be undressed and a thorough body wash should be given which prevents more than 85% of pesticide absorption and antidote should be given simultaneously.

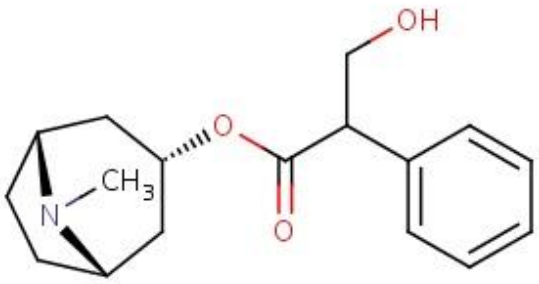
Health care providers self protection and decontamination should be given first priority in OP and nerve agent treatment. Adequate training should be given to all the medical personnel participating in the treatment of organophosphor poisoning. These health care providers should be adequately trained about safety precautions and they should be provided with neoprene gloves and eye goggles.

There is a controversy remains regarding Gastro intestinal tract decontamination. WHO recommends activated charcoal should be given in case of insecticide poisoning.

Activated charcoal

Anti-cholinergic agents:

Atropine is the main antidote therapy for pesticide poisoning. Atropine effectively crosses the blood brain barrier and it reverses the central and peripheral muscuranic effects. Atropine is given in the dose of 2 mg loading followed by double the dose for every five minutes which yeild a dose of 25 mg in 20 minutes and 75mg in 25 minutes. Atropine should be give till signs of atropinisation like disappearance of crackles in longs, heart rate more than 90/in and stable blood pressure



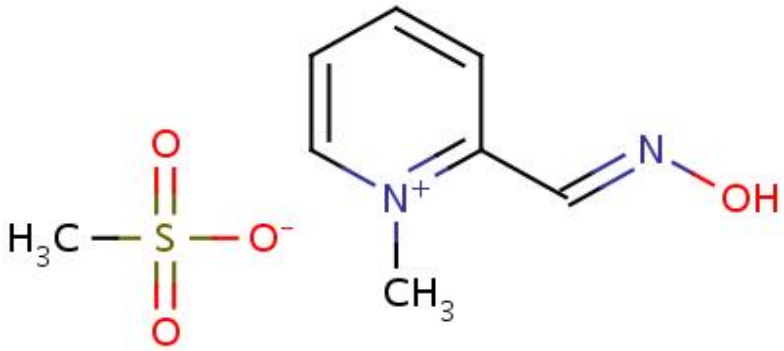
Chemical structure of atropine

Oximes:

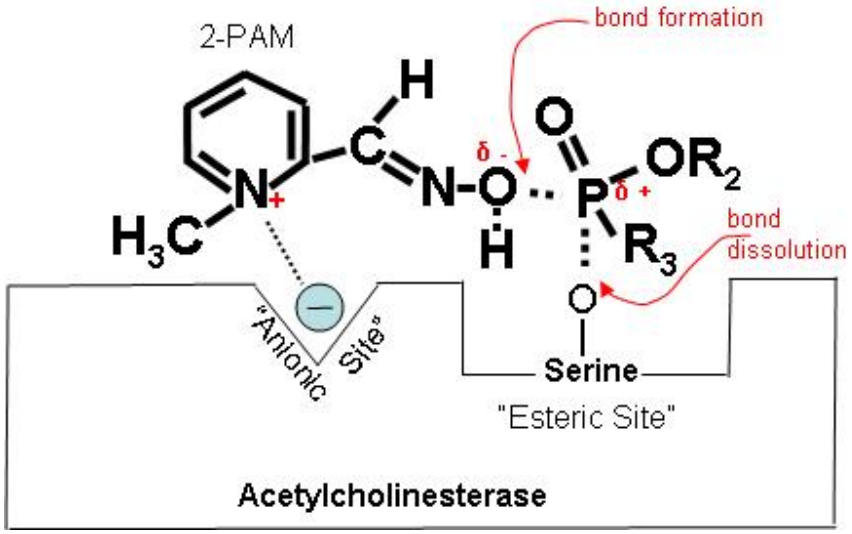
Oximes: The enzyme acetylcholinesterase is inhibited by Organophosphorus. Oximes are useful in the reactivation of acetylcholinestrase. Pralidoxime was first introduced in middle of 1950 and it was first used in the treatment of parathion poisoning. Though other oximes like obidoxime were introduced, till now, only pralidoxime is widely used. Pralidoxime exists in four types of salts of which most commonly used is chloride and iodide salts. Chloride is preferred for iodide because it does not affect thyroid gland and it's molecular weight is less and it is five times potent than iodide salt.

Pralidoxime effectiveness largely depends on type and amount of pesticide consumed. The effectiveness was doubted by a study[19] conducted in Christian Medical College which shows low dose of pralidoxime infusion is harmful, but there may be bias in selecting the patient group, type of compound consumed and time delay in treatment.

Chemical structure of pralidoxime



Mechanism of action of pralidoxime

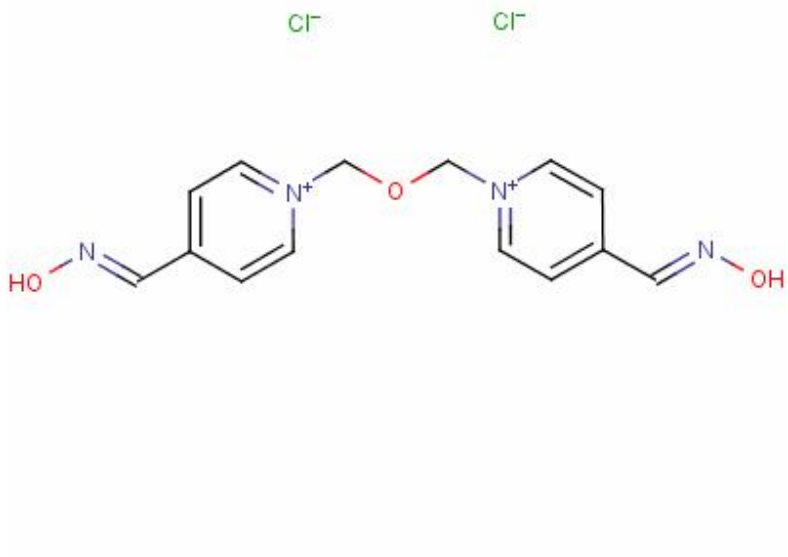


Any oximes whether it is pralidoxime or obidoxime it should be given before the onset of aspiration pneumonitis or before development of hypoxic ischemic encephalopathy.

WHO recommends first a loading dose of pralidoxime of 2gms should be given over one hour. Loading dose should be given slowly otherwise it will cause severe vomiting and thereby increasing the risk of aspiration and other side effects like tachycardia and increase in diastolic hypertension can occur. Following loading dose pralidoxime should be maintained at a dose of 500mg/hour for at least three days.

Obidoxime is usually given by intravenous route. If intravenous access is not possible, it can be given by intramuscular route. Dose is 250 mg bolus followed by 750 mg/24 hour maintenance dose given to attain a serum level of 20 micro moles/L. The common side effects of this compound include nausea, headache, dizziness, paraethesia and pallor.

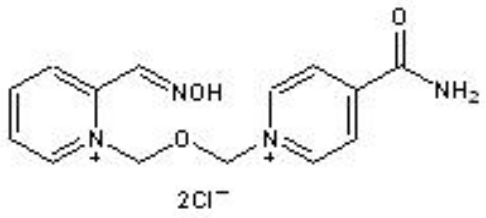
Chemical structure of obidoxime



Asoxime is given in two doses as either 250 mg or 500 mg intramuscular injection and it reaches the plasma concentration of 4mg/l in 4-6 mins which is maintained for 125 mins in case of low dose and 200 mins in case of high dose. It is given as i.m. injection four times a day along with atropine for 2-6 days.

A study[20] done on twenty two healthy individuals didn't reveal any side effects when asoxime was given in the dose of 500 mg per oral. Asoxime is a promising bispyridinium in the medical management following poisoning with many nerve agents. The drawback of asoxime when compared with other oximes is

the lack of stability in the aqueous solution. Asoxime is an effective antidote for insecticide poisoning except in cases with complications like HIE or aspiration pneumonitis, which is common in fast acting insecticides like parathion.



Chemical structure of asoxime.

Prevention of OP Poisoning:

1. Prevention of insecticide poisoning is better than treatment because of risk in treatment and high fatality rate;

2. There should be adequate ventilation and enough air circulation in the field of insecticide spraying;

3. Don’t use the insecticide for indoor spraying if it was supposed to be used for outdoor purpose only;

4. Follow the safety precautions in the product label;

5. Always try to use the products which are premixed;

6. Always keep the food products and drinking water away from the area of vicinity of insecticide spraying;

7. Always thoroughly wash the fruits and vegetables before using;

8. Don’t use or recycle the insecticide containers for storing food and related products;

9. Don’t store the insecticides in other containers;

10. Use protective googles and gloves while spraying insecticides;

11. Wash your hand with soap water after spraying insecticides;

12. Always store the insecticides in a separate store room and should be out of reach for children;

13. Educate the children adequately about insecticides and its poisoning; and

14. Never dispose the insecticides and its remain in toilet or water drain, ponds and river.

MATERIAL AND METHOD

1. Patients admitted in general medicine department chengalpattu.

2. Information collected through a preformed and pretested proforma.

3. Qualifying patients will undergo a detailed history, clinical examination and biochemical analysis.

4.The propotions of the complications and mortality will be calculated using the student T test for statiscal significance. SPSS/EPI INFO will be used for statistical analysis.

RESULTS

Table 4 :Distribution of patients according to their age group (N=110)

Bio-social characteristics	No	Percent
Age in years		
20-40	61	55.45
40-60	35	31.81
>60	14	12.72
Range	21-75	

Chart 1: Distribution of patients according to their age group.

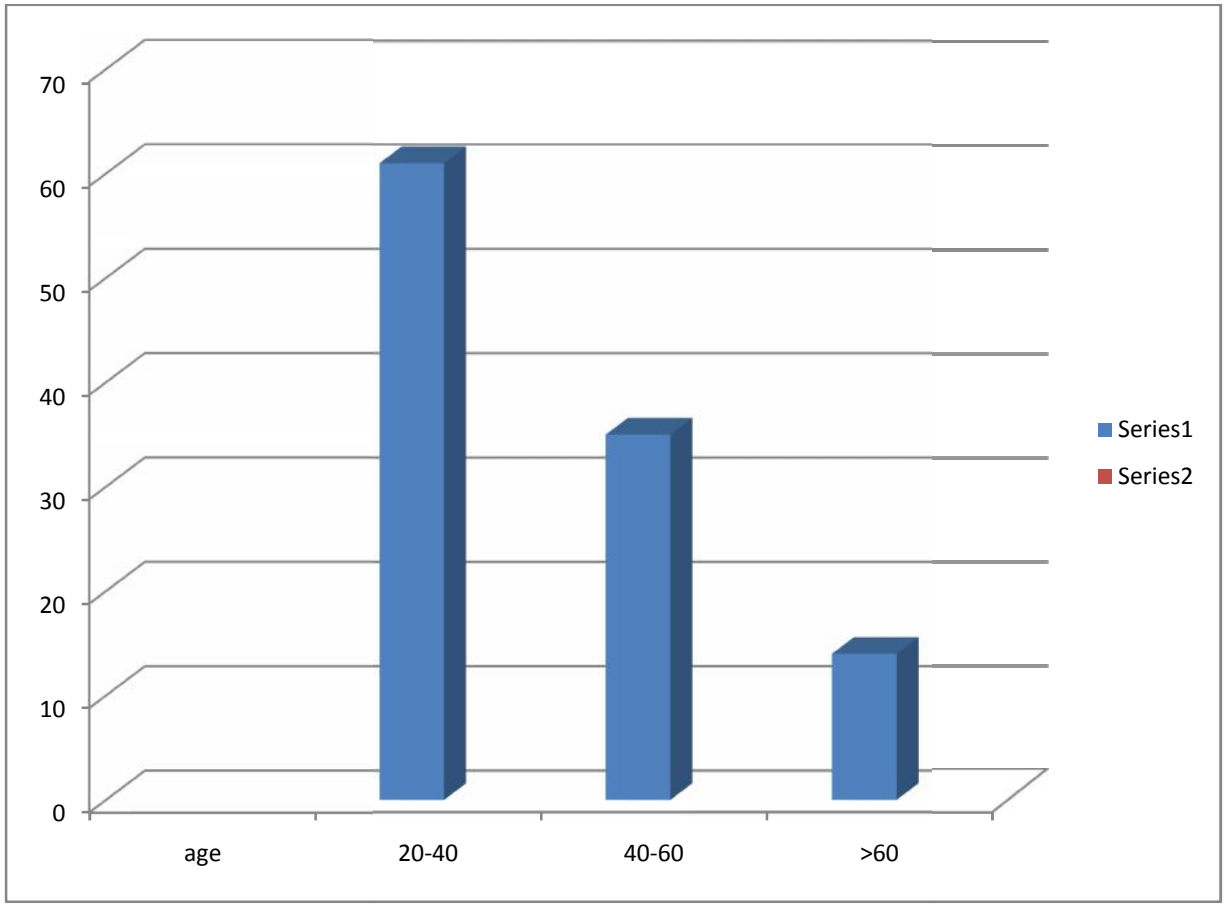
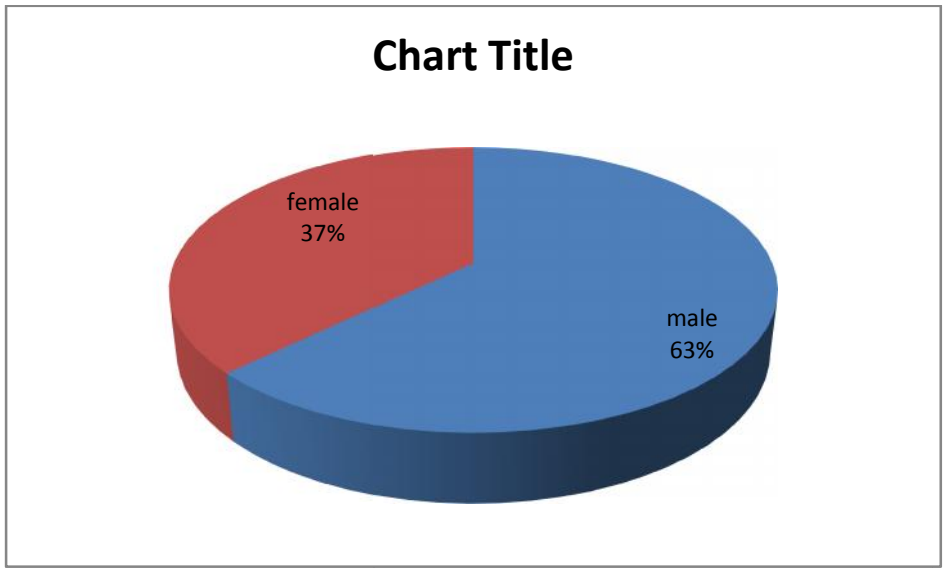


Table 5 :Distribution of patients according to their sex (N=110)

Characteristics	No	Percent
Male	69	62.72
Female	41	37.27

Chart 2 :Distribution of patients according to their sex

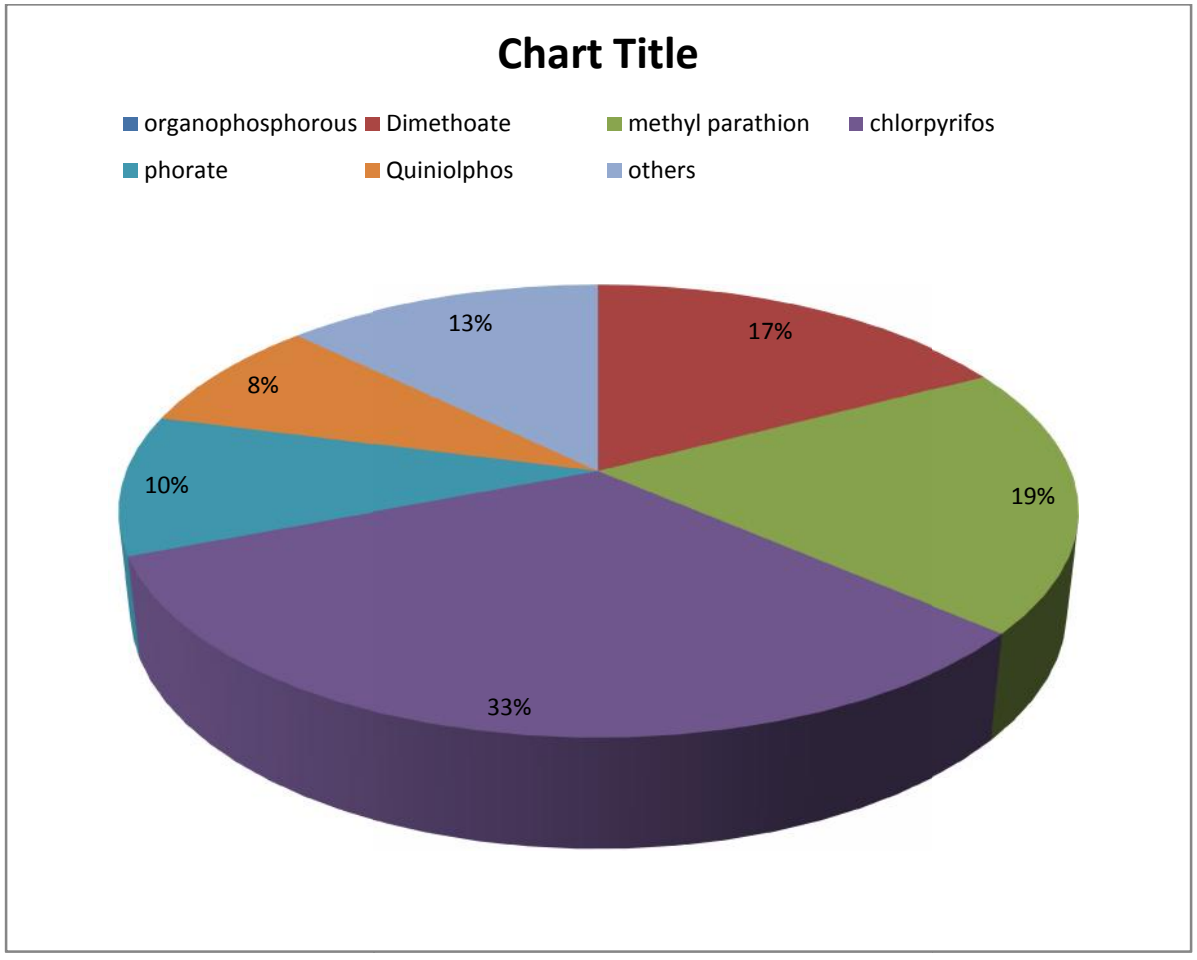


This study was done in Chengalpattu Medical College between above mentioned duration with incidence of organophosphorus poisoning common among males compared to females. Majority of patients were in the age group of 20-40 years.

Table 6:Distribution of patients according to the type of organophosphorus compound consumed(N=110)

Type of organophosphorus compound	No.	Percent
Chlorpyriphos	36	32.72
Dimethoate	19	17.27
Methyl parathion	21	19.09
Phorate	11	10
Quiniolphos	9	8.18
Others	14	12.72

Chart 3 :Distribution of patients according to the type of organophosphorus compound consumed

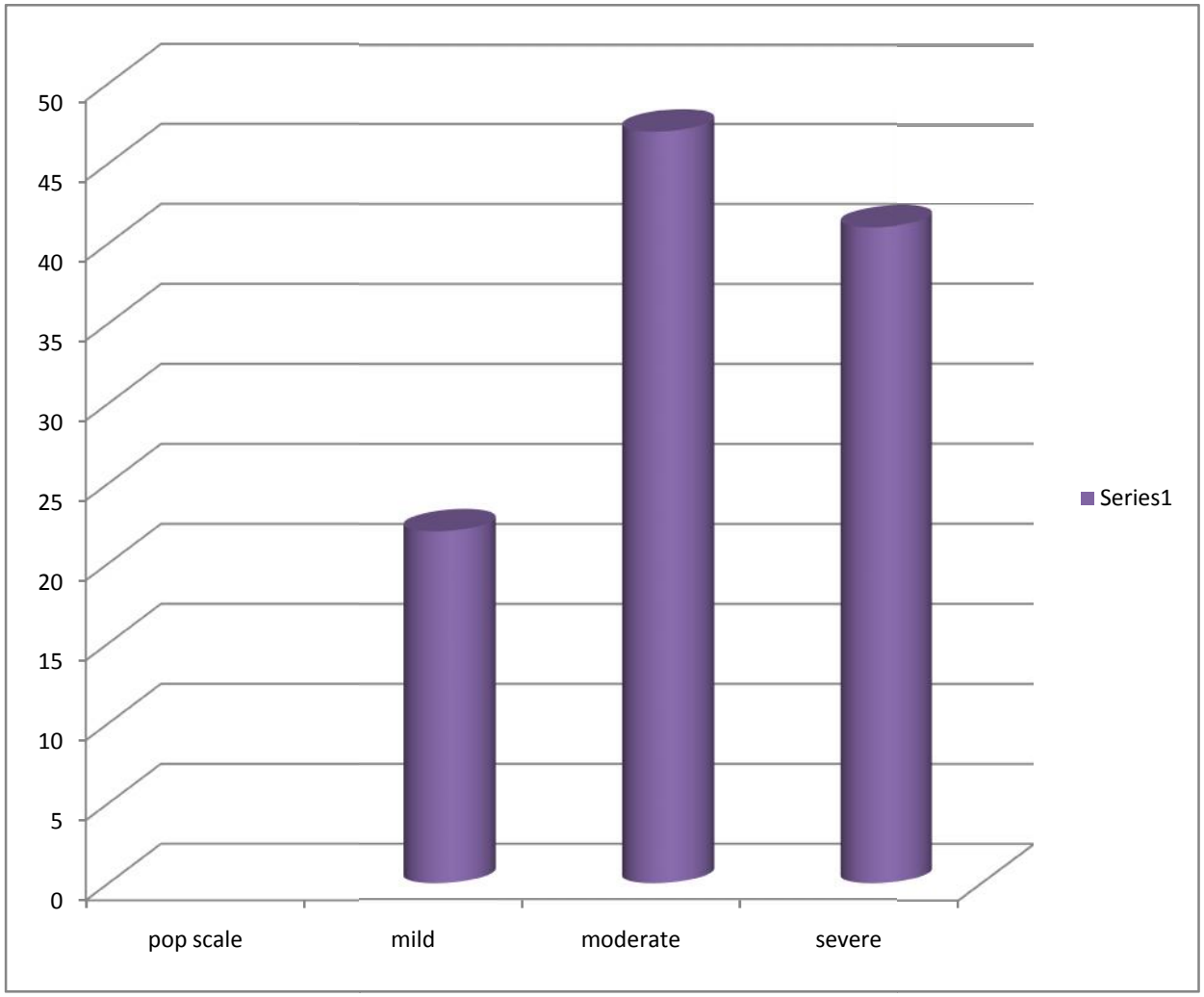


Most common compound consumed was chlorpyriphos(32.72%)

Table 7:Distribution of patients according to their peradeniya score(N=50)

Peradeniya score	No	Percent
Mild	22	20
Moderate	47	42.72
Severe	41	37.27

Chart 4 :Distribution of patients according to their peradeniya score



Majority of patients had a moderate severity of organophosphorus poisoning at presentation.

Table 8:Distribution of patients according to their occupation(N=110)

Occupation	No	Percent
Student	15	13.63
Housewife	33	30
Farmer	42	38.18
Employee	15	13.63
None	5	4.5

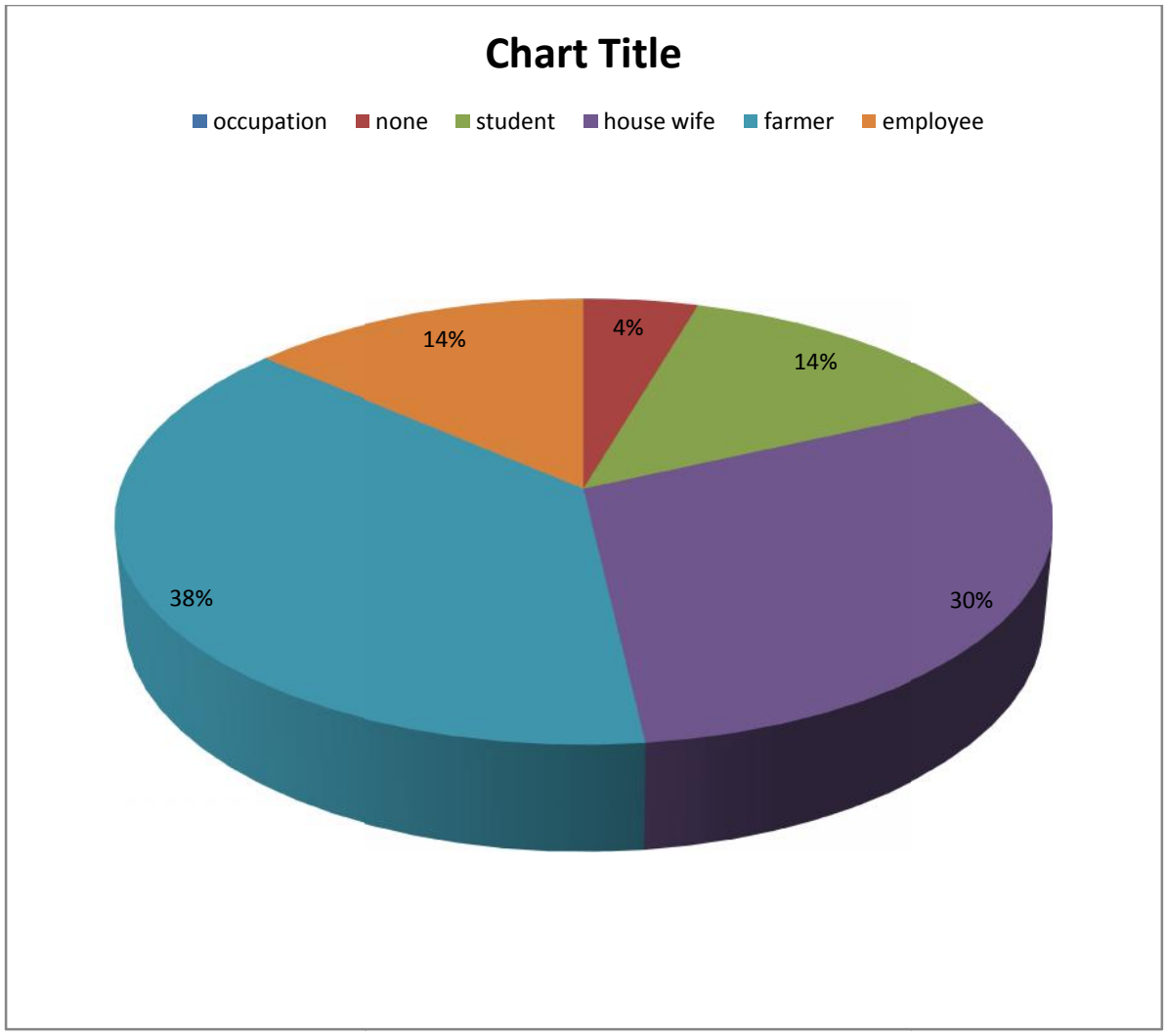


Chart 5: distribution of patients according to their occupation.

Majority of patients who consumed organophosphorus poisoning were farmer by occupation.

Table 9 :Distribution of patients according to their residence

Residence	No	Percent
Rural	73	66.36
Urban	37	33.63

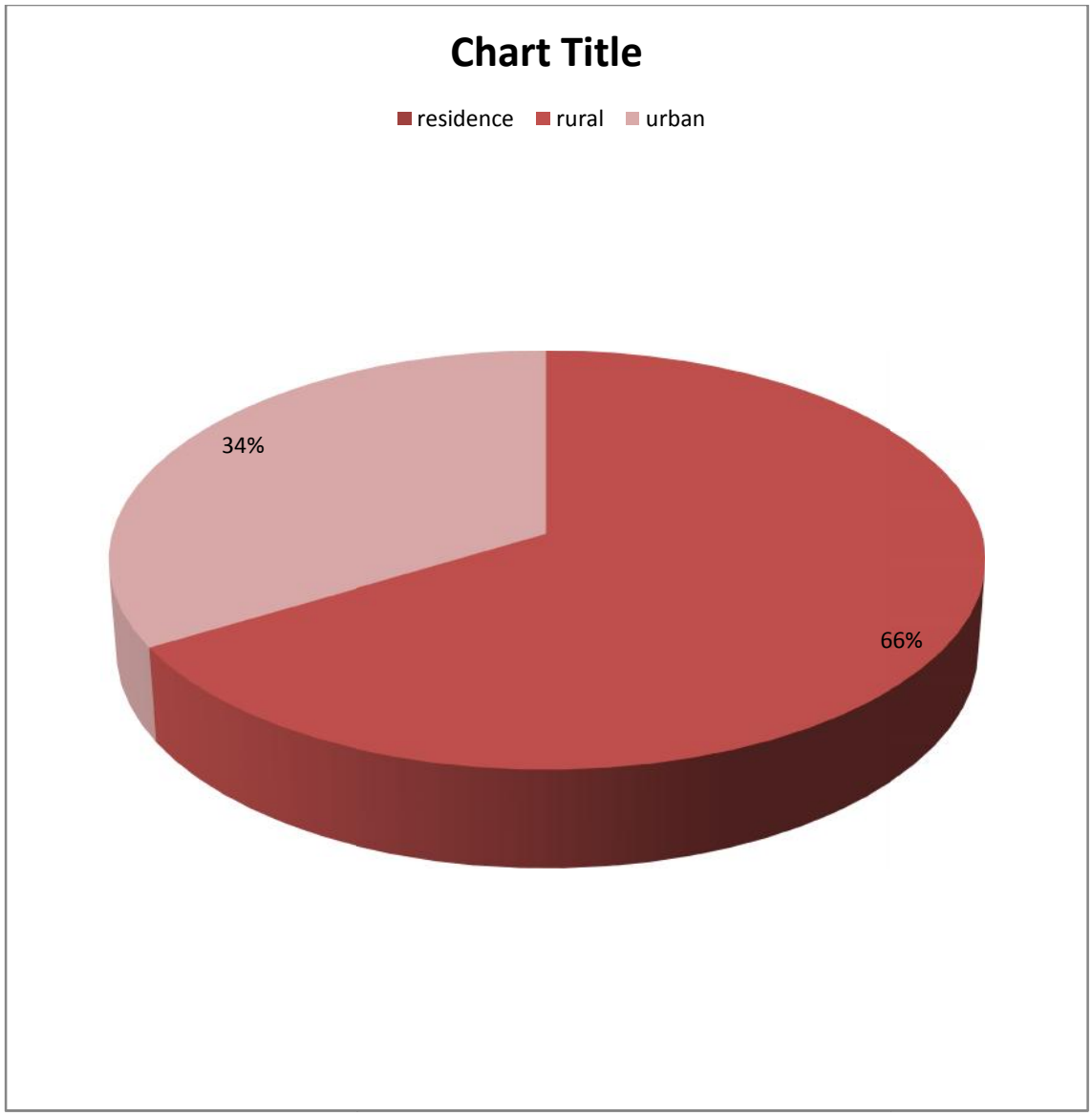


Chart 6: distribution of patients according to their residence.

Majority of patients who consumed organophosphorus poisoning were from rural area.

Table 10 :Distribution of patients according to their route of administration

Route	No	Percent
Oral	92	83.63
Inhalation	11	10
Others	7	6.36

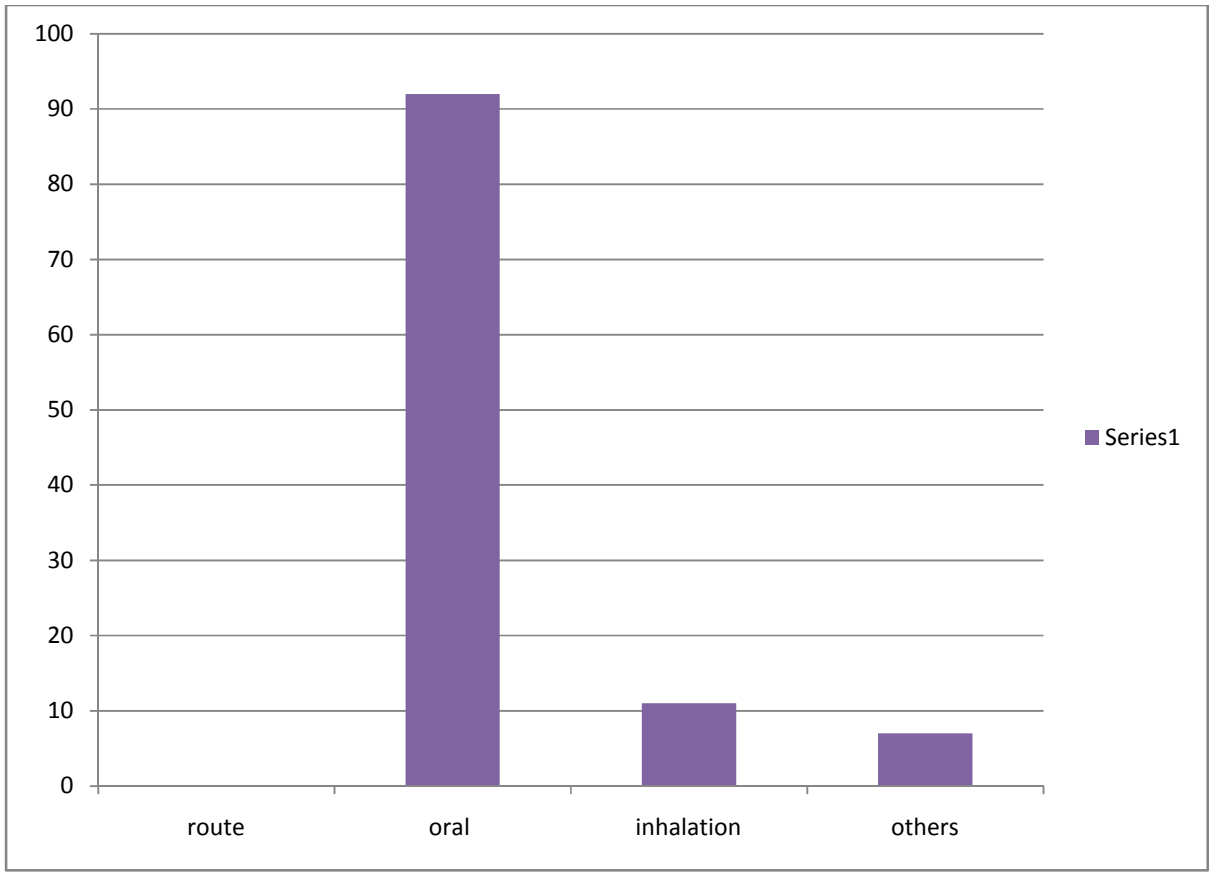


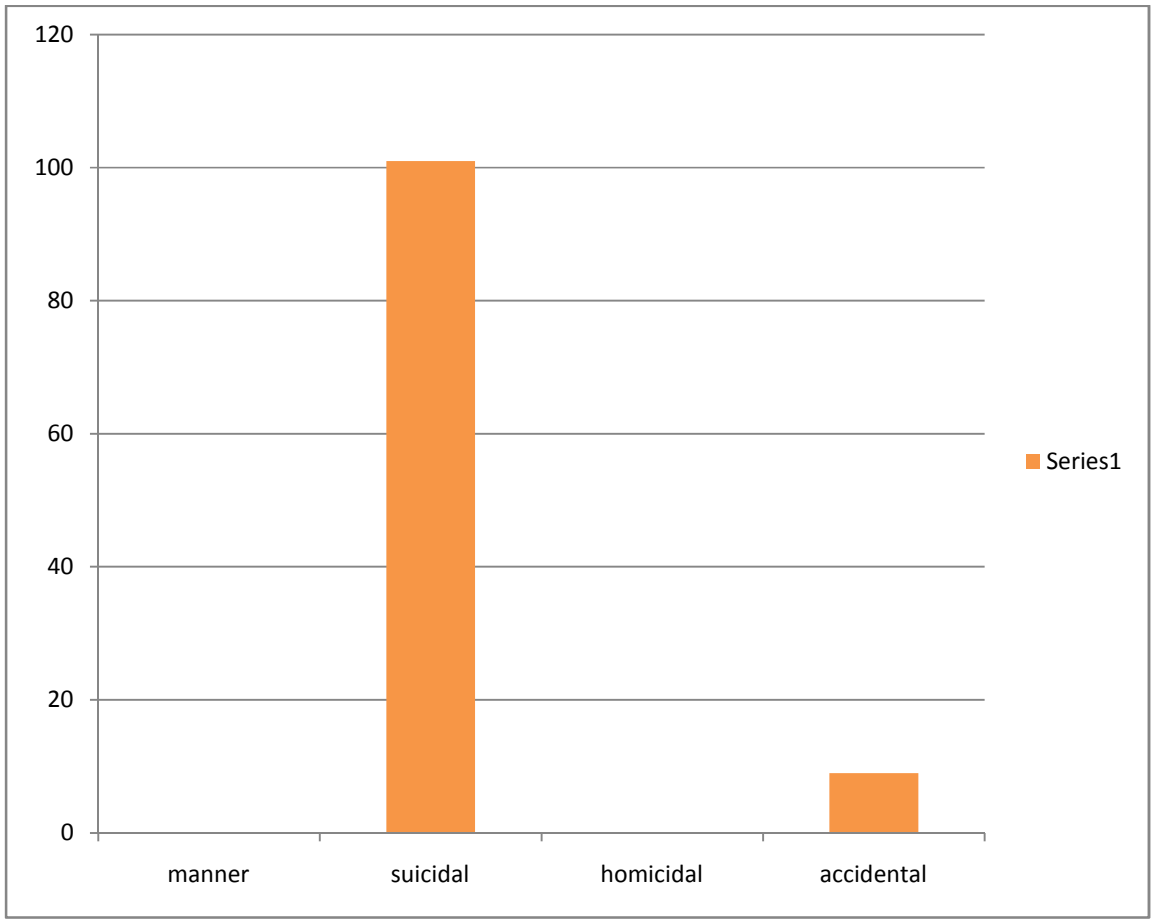
Chart 7 : distribution of patients according to their route of administration.

Route of administration of organophosphorus poisoning in majority of patients was oral.

Table 11:Manner of distribution of organophosphorus poisoning

Manner	No	Percent
Suicidal	101	91.81
Homicidal	0	0
Accidental	9	8.18

Chart 8 :manner of distribution of organophosphorus poisoning.



In majority of cases manner of distribution of organophosphorus poisoning is suicidal.

Table 12: Distribution of patients according to the clinical features

Signs and Symptoms	No	Percent
Sweating	27	24.54
Vomiting	44	40
Diarrhea	76	69.09
Salivation	41	37.27
bradycardia	32	29.09
Miosis	98	89.09
Fasiculation	40	36.36
Abdominal pain	95	86.36
neck muscle weakness	16	14.54

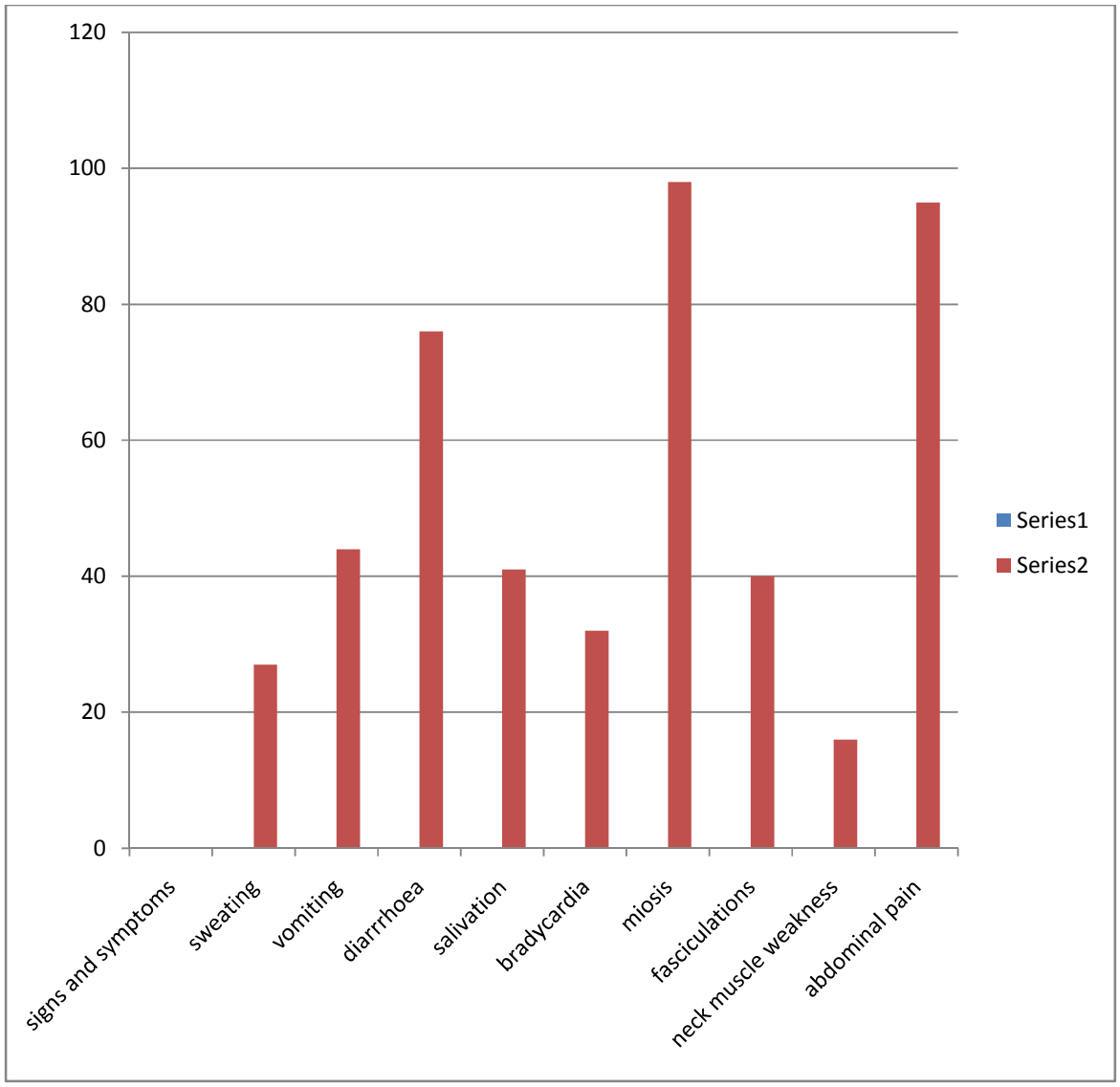


Chart 9: distribution of patients according to their symptoms

Most common clinical finding in patients was miosis followed by abdominal pain and diarrhea.

Table 13:Association of mild severity by peradeniya score of organophosphorus(POP) with CPK,SGOT and SGPT.

pop		CPK	SGOT	SGPT
1mild	Mean	79.5000	38.6364	45.0000
	N	22	22	22
	Std. Deviation	27.9570	15.5059	16.1923
	Minimum	29.00	14.00	10.00
	Maximum	121.50	76.00	73.00
	Range	92.50	62.00	63.00

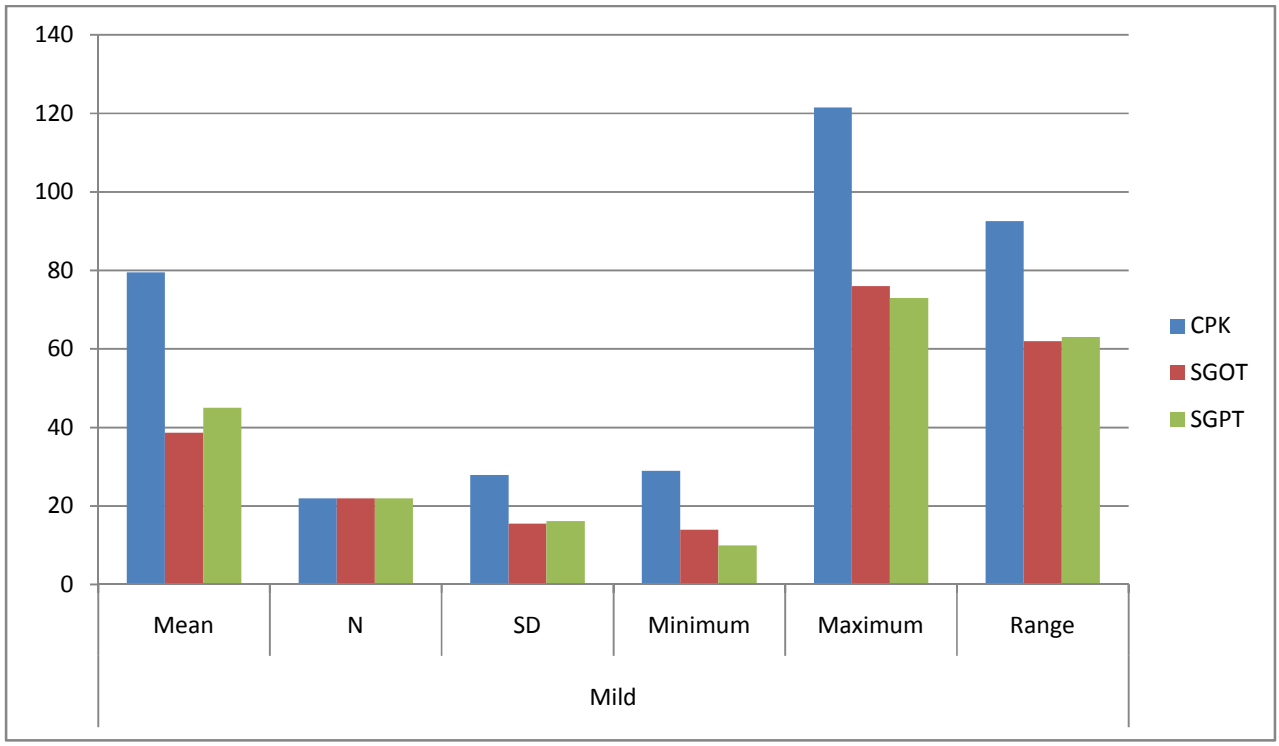


Chart10 : Association of mild severity by peradeniya score of organophosphorus(POP) with CPK,SGOT and SGPT

Table 14:Association of moderate severity by peradeniya score of organophosphorus(POP) with CPK,SGOT and SGPT.

2moderate	Mean	249.24	71.5319	70.4468
	N	47	47	47
	Std. Deviation	52.7748	29.5590	26.0291
	Minimum	133.50	19.00	26.00
	Maximum	387.50	150.00	146.00
	Range	254.00	131.00	120.00

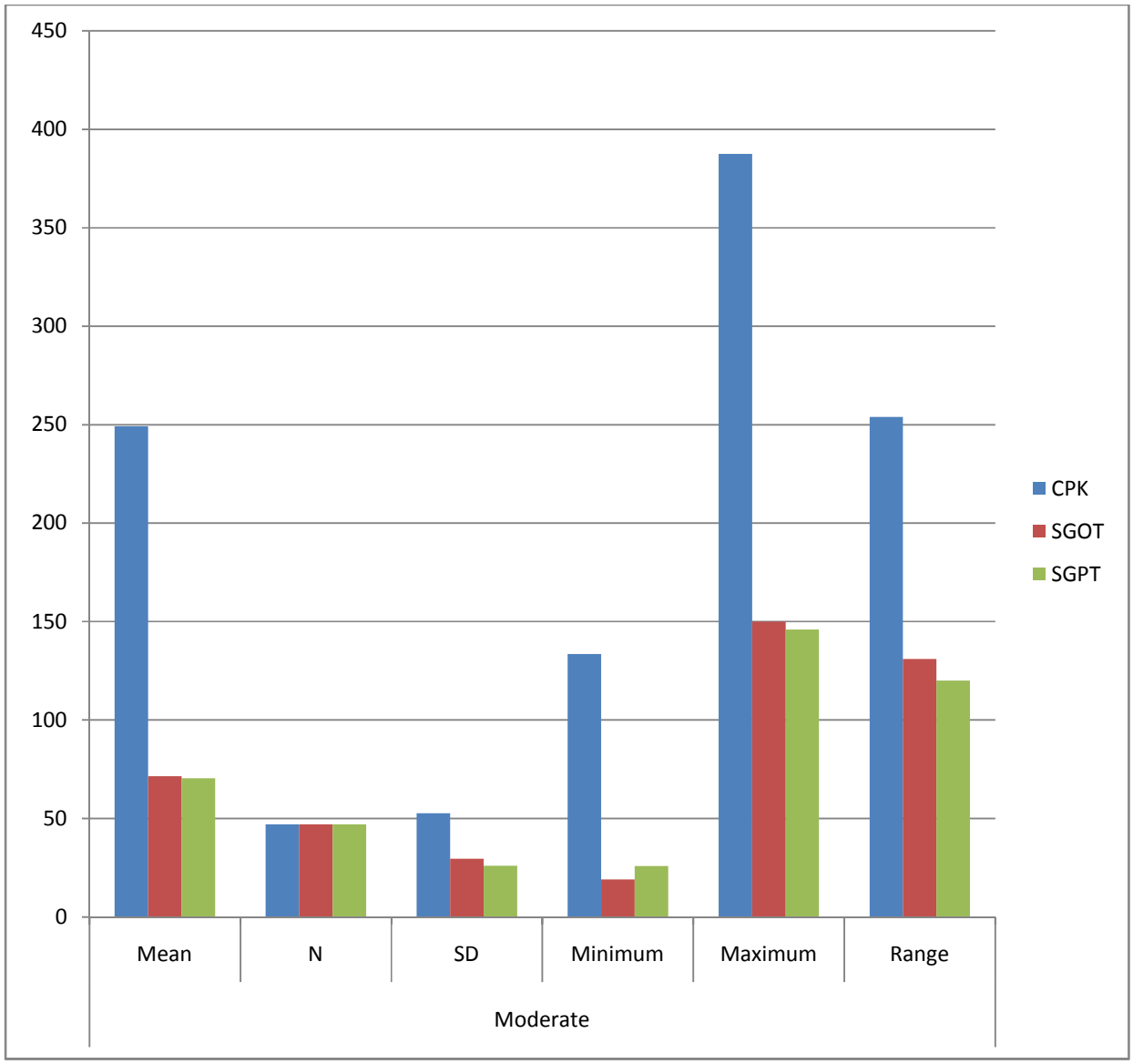


Chart 11: Association of moderate severity by peradeniya score of organophosphorus(POP) with CPK,SGOT and SGPT.

Table 15: Association of severe severity by peradeniya score of organophosphorus(POP) with CPK,SGOT and SGPT.

3severe	Mean	843.68	157.54	138.32
	N	41	41	41
	Std. Deviation	13.0205	52.7101	49.1322
	Minimum	564.50	32.00	33.00
	Maximum	1100.00	301.00	288.00
	Range	535.50	269.00	255.00

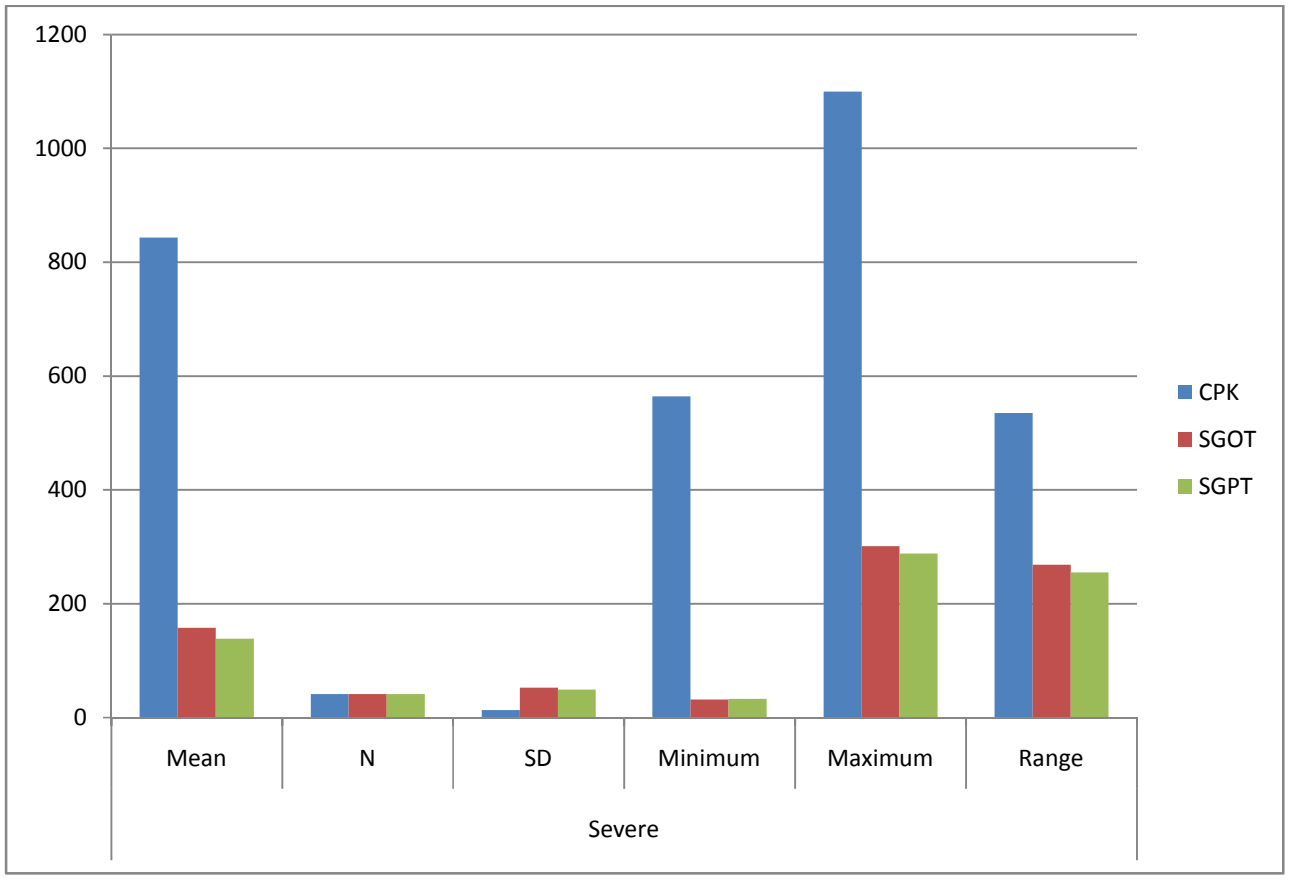


Chart 12: Association of severe severity by peradeniya score of organophosphorus(POP) with CPK,SGOT and SGPT.

pop * levels cpk Crosstabulation

			CPK LEVELS		
			NORMAL (24-195)	ABNORMAL (>195)	Total
pop	mild	Count	22	0	22
		% within pop	100.0%	.0%	100.0%
		% within levels cpk	73.3%	.0%	20.0%
		% of Total	20.0%	.0%	20.0%
	moderate	Count	8	39	47
		% within pop	17.0%	83.0%	100.0%
		% within levels cpk	26.7%	48.8%	42.7%
		% of Total	7.3%	35.5%	42.7%
	severe	Count	0	41	41
		% within pop	.0%	100.0%	100.0%
		% within levels cpk	.0%	51.2%	37.3%
		% of Total	.0%	37.3%	37.3%
Total		Count	30	80	110
		% within pop	27.3%	72.7%	100.0%
		% within levels cpk	100.0%	100.0%	100.0%
		% of Total	27.3%	72.7%	100.0%

Table 16:POP* levels of CPK crosstabulation.

pop * level sgot Crosstabulation

			SGOT LEVEL		
			normal (5 TO 40)	abnormal>40	Total
pop	mild	Count	17	5	22
		% within pop	77.3%	22.7%	100.0%
		% within level sgot	68.0%	5.9%	20.0%
		% of Total	15.5%	4.5%	20.0%
	moderate	Count	7	40	47
		% within pop	14.9%	85.1%	100.0%
		% within level sgot	28.0%	47.1%	42.7%
		% of Total	6.4%	36.4%	42.7%
	severs	Count	1	40	41
		% within pop	2.4%	97.6%	100.0%
		% within level sgot	4.0%	47.1%	37.3%
		% of Total	.9%	36.4%	37.3%
Total		Count	25	85	110
		% within pop	22.7%	77.3%	100.0%
		% within level sgot	100.0%	100.0%	100.0%
		% of Total	22.7%	77.3%	100.0%

Table 17 :POP *levels of SGOT crosstabulation

pop * level sgpt Crosstabulation

			SGPT LEVEL		
			normal (7 TO 56)	Abnormal >56	Total
pop	mild	Count	17	5	22
		% within pop	77.3%	22.7%	100.0%
		% within level sgpt	48.6%	6.7%	20.0%
		% of Total	15.5%	4.5%	20.0%
	moderate	Count	15	32	47
		% within pop	31.9%	68.1%	100.0%
		% within level sgpt	42.9%	42.7%	42.7%
		% of Total	13.6%	29.1%	42.7%
	severs	Count	3	38	41
		% within pop	7.3%	92.7%	100.0%
		% within level sgpt	8.6%	50.7%	37.3%
		% of Total	2.7%	34.5%	37.3%
Total		Count	35	75	110
		% within pop	31.8%	68.2%	100.0%
		% within level sgpt	100.0%	100.0%	100.0%
		% of Total	31.8%	68.2%	100.0%

Table 18 : POP*levels of SGPT crosstbulation.

Correlations

		POP	CPK	SGOT	SGPT
pop	Pearson Correlation	1	.914**	.759**	.709**
	Sig. (2-tailed)		.000	.000	.000
	N	110	110	110	110
cpk	Pearson Correlation	.914**	1	.806**	.759**
	Sig. (2-tailed)	.000		.000	.000
	N	110	110	110	110
sgot	Pearson Correlation	.759**	.806**	1	.985**
	Sig. (2-tailed)	.000	.000		.000
	N	110	110	110	110
sgpt	Pearson Correlation	.709**	.759**	.985**	1
	Sig. (2-tailed)	.000	.000	.000	
	N	110	110	110	110

**. Correlation is significant at the 0.01 level (2-tailed).

Table 19: correlation of POP with levels of CPK,SGOT and SGPT.

Crosstab

			pro cpk	
			abnormal(>195)	Total
prognosis	Respiratory failure	Count	19	19
		% within pro cpk	59.4%	59.4%
		% of Total	59.4%	59.4%
	Intermediate syndrome	Count	5	5
		% within pro cpk	15.6%	15.6%
		% of Total	15.6%	15.6%
	death	Count	8	8
		% within pro cpk	25.0%	25.0%
		% of Total	25.0%	25.0%
Total		Count	32	32
		% within pro cpk	100.0%	100.0%
		% of Total	100.0%	100.0%

Table 20 : prognosis vs CPK levels crosstab.

			PRO SGPT		
			Normal (7 TO 56)	Abnormal >56	Total
prognosis	Respiratory failure	Count	1	18	19
		% within prosgpt	100.0%	58.1%	59.4%
		% of Total	3.1%	56.2%	59.4%
	Intermediate syndrome	Count	0	5	5
		% within prosgpt	.0%	16.1%	15.6%
		% of Total	.0%	15.6%	15.6%
	death	Count	0	8	8
		% within prosgpt	.0%	25.8%	25.0%
		% of Total	.0%	25.0%	25.0%
Total		Count	1	31	32
		% within prosgpt	100.0%	100.0%	100.0%
		% of Total	3.1%	96.9%	100.0%

Table 21 : prognosis vs SGOT crosstab.

Crosstab

			PRO SGOT abnormal >40	Total
prognosis	Respiratory failure	Count	19	19
		% within pro sgot	59.4%	59.4%
		% of Total	59.4%	59.4%
	Intermediate syndrome	Count	5	5
		% within pro sgot	15.6%	15.6%
		% of Total	15.6%	15.6%
	death	Count	8	8
		% within pro sgot	25.0%	25.0%
		% of Total	25.0%	25.0%
Total		Count	32	32
		% within pro sgot	100.0%	100.0%
		% of Total	100.0%	100.0%

Table 22 : prognosis vs SGPT crosstab.

Table 23 :Association of respiratory failure in organophosphorus poisoning with CPK,SGOT and SGPT.

PROGNOSIS		CPK	SGOT	SGPT
Respiratory failure	Mean	815.1053	157.8421	141.5789
	N	19	19	19
	Std. Deviation	223.841	40.23578	36.19441
	Minimum	241.50	67.00	45.00
	Maximum	1100.00	211.00	198.00
	Range	858.50	144.00	153.00

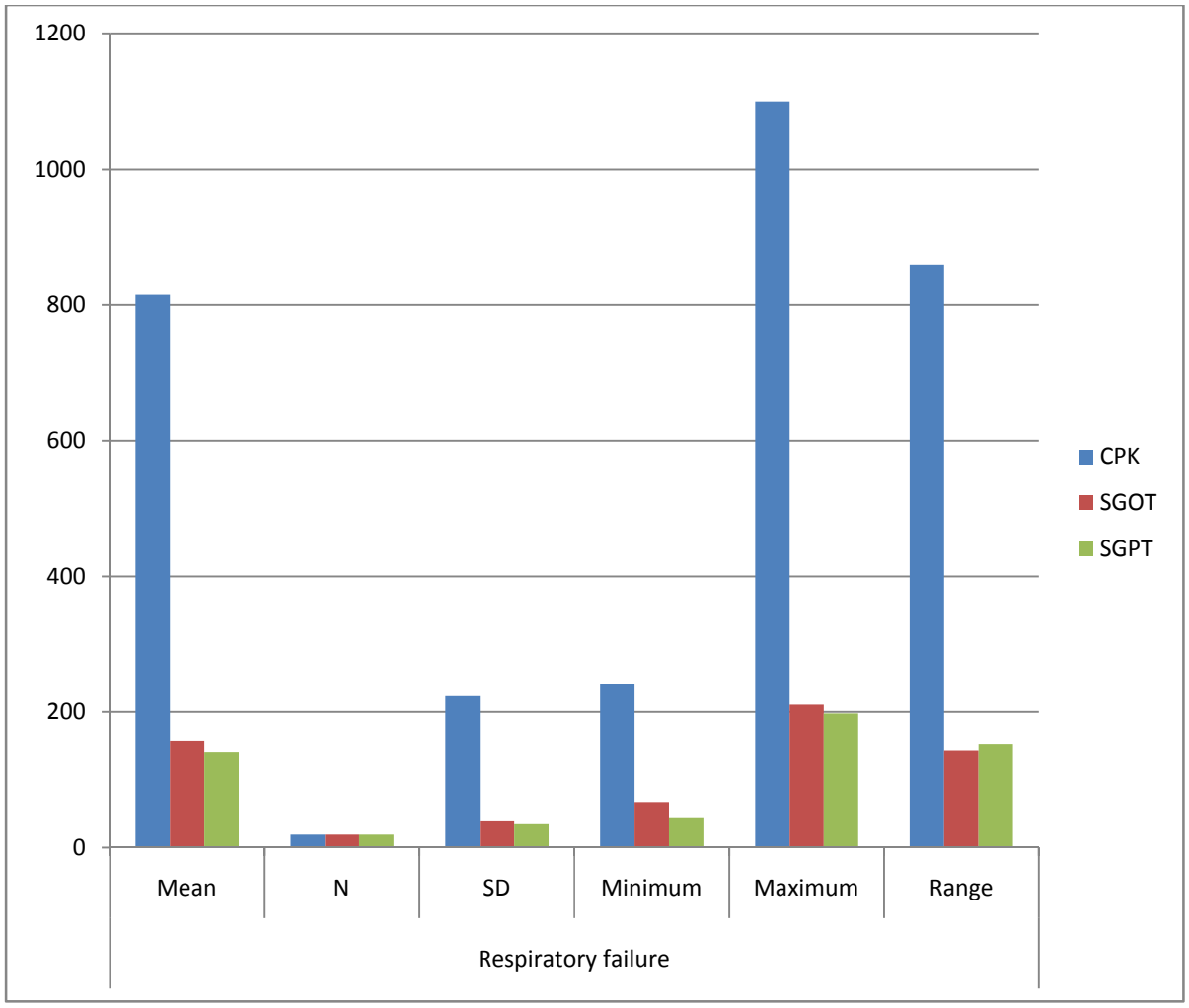


Chart 13: Association of respiratory failure in organophosphorus poisoning with CPK,SGOT and SGPT.

Table 24:Association of intermediate syndrome in organophosphorus poisoning with CPK,SGOT and SGPT.

Intermediate syndrome	Mean	857.2000	159.4000	143.4000
	N	5	5	5
	Std. Deviation	74.99133	39.75299	35.76031
	Minimum	770.00	98.00	86.00
	Maximum	955.00	198.00	176.00
	Range	185.00	100.00	90.00

Chart 14: Association of intermediate syndrome in organophosphorus poisoning with CPK,SGOT and SGPT.

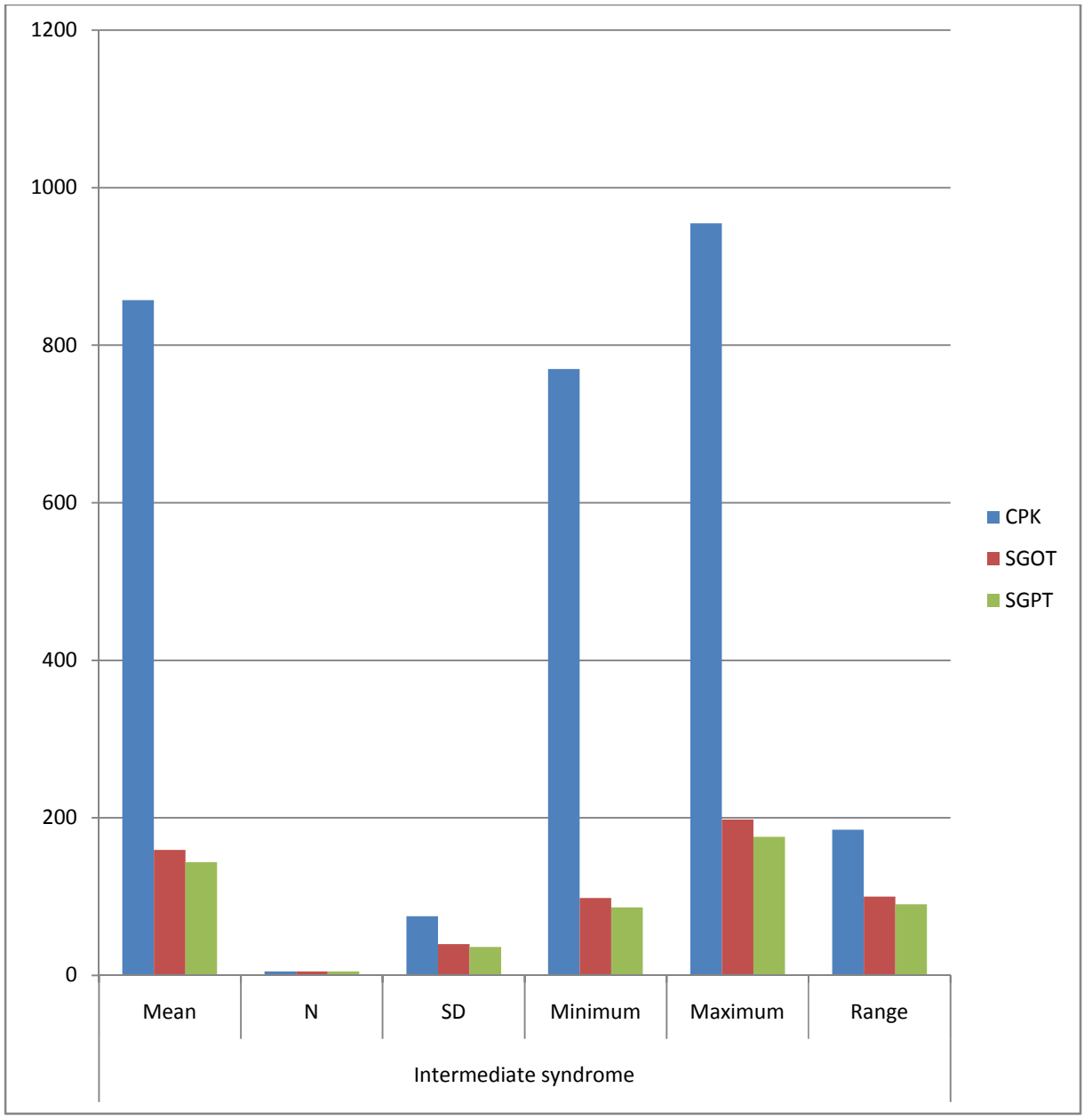


Table 25:Association of death in organophosphorus poisoning with CPK,SGOT and SGPT.

death	Mean	940.8125	185.3750	160.3750
	N	8	8	8
	Std. Deviation	108.348	24.07095	25.24134
	Minimum	788.50	156.00	135.00
	Maximum	1100.00	211.00	198.00
	Range	311.50	55.00	63.00

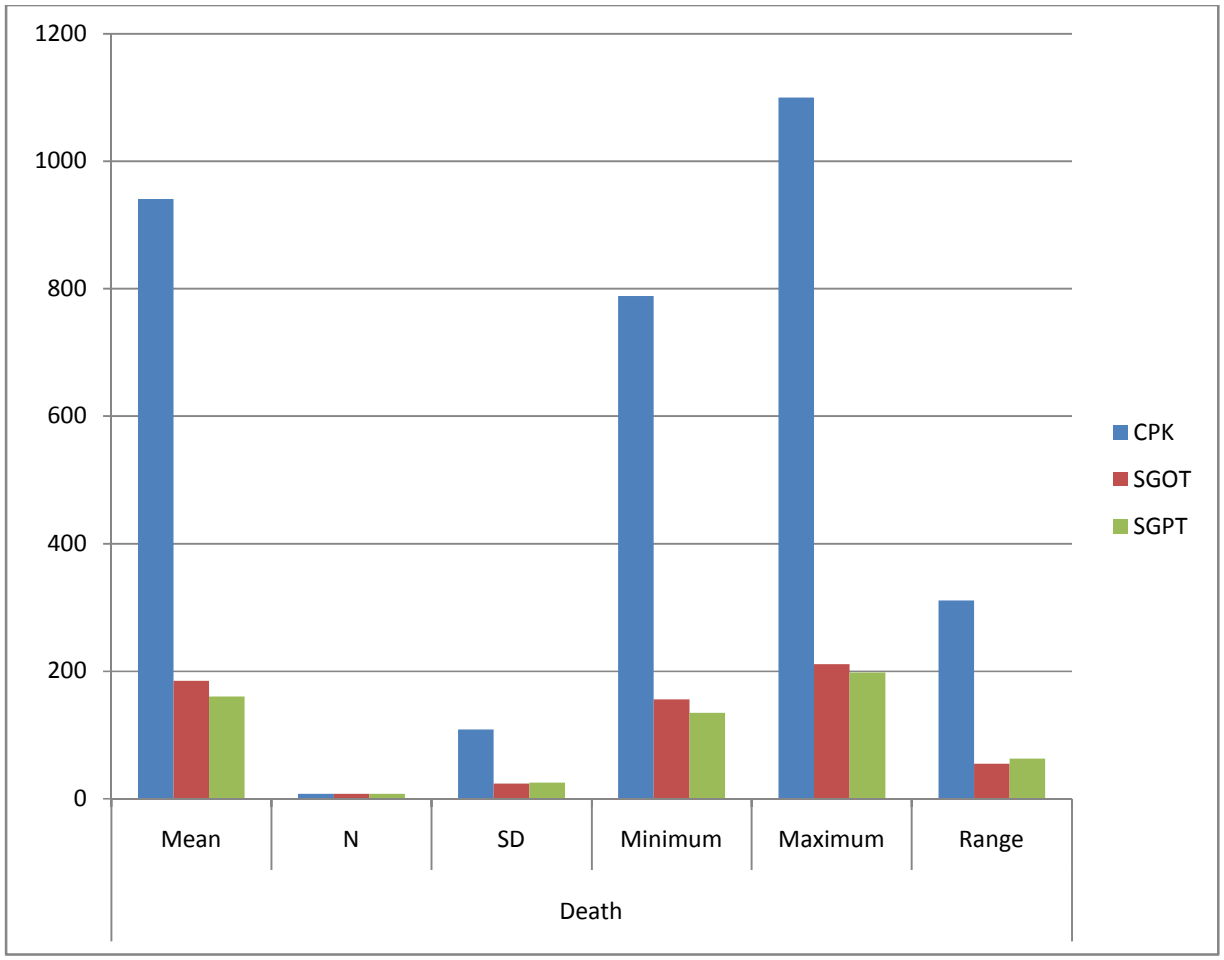


Chart 15 : Association of death in organophosphorus poisoning with CPK,SGOT and SGPT

Discussion

Organophosphorus (OP) compounds are among the most commonly used pesticides in agriculture. Because of their wide use and easy accessibility, OP toxicity is important global health problem especially in many developing countries like India.

The major toxicity of organophosphorus poisoning is due to the inhibition of acetylcholinesterase and there by leading to the excess stimulation of muscuranic and nicotinic receptors. Cholinergic symptoms develop fast which forms the basis for clinical diagnosis which is confirmed by cholinesterase inhibition. Cholinesterase levels are not done in all clinical labs and it is not available in many parts of India, where clinical case load is very high. Present study showed that out of 110 patients, 62.72% were males and 37.27% were females. This study correlated well with study done by Dash et al.'s[21] study, which showed an incidence of 67% in males and 23% in females.

They were aged from 21 to 73 years, 66% came from rural areas, whereas 34% from urban areas. Regarding occupation, 13.63% were students, 30% housewives and 38.18% farmers. The most common route of exposure was oral

route (83.63%), the most common manner of poisoning was suicidal manner (91.1%), and the commonest OP compound was Chlorpyriphos (32.72%). **Weissmann-Brenner et al**[22] reported that 66% of patients with OP poisonings were males and 34% were females, 39% were less than 10 years old, 64% of exposure was accidental, 36% was suicidal and the most common route of intoxication was oral (67%).

The present study illustrated that most of patients manifested with miosis (89%), followed by abdominal pain (86%), diarrhea (69.09%) and vomiting (40%). Increase of Sr. CPK levels reflects injury to a tissue of high CPK activity. CPK level measurements are useful in the diagnosis of medical conditions like myocardial infarction and skeletal muscle injuries, which are acute. Theories relate this increased CPK levels to agitation, hyperactivity and drugs (i.e. rhabdomyolysis and muscle necrosis). The present study showed that there was a high degree of correlation between the initial serum CPK levels and the severity of acute OP poisoning; as illustrated by the positive correlation of initial serum CPK level with POP scale. These correlations were found to be statistically highly significant ($P < 0.001$).

These results are in agreement with **Bhattacharyya** et al[23] who confirmed the presence of a high degree of correlation between initial CPK value and POP scale. Muscle fiber necrosis and consequently raised CPK levels occur in severely acute OP poisoned cases. So, cheaper, easily quantifiable and more available biochemical markers in relation to OP poisoning like serum CPK can be used in predicting as well as assessing the prognosis of patients with OP poisoning.

All the patients included in the study were classified according to Peradeniya organophosphorus poisoning scale into mild (0-3), moderate (4-7) and severe (8-11).Of the 110 patients who were studied 22 (20%) had mild, 47 (42.72%) had moderate and 41(37.27%) had severe level of poisoning.

The mean age group in the mild (36 years) and moderate (32.02 years) severity patients were similar. However the mean age group in the severe age group was 51.48 years, suggesting that the older age group have a severe degree of poisoning. There was not much variation in distribution of severity between males and females. The severity of OP poisoning in this study ranged from mild, moderate and severe; most of cases were presented with moderate OP toxicity.

Various authors Illustrated that the POP scale can efficiently predict the severity of OP poisoned patients. Muscle injury in insecticide poisoning occurs in three types. Type 1 is because of continuous depolarization at NM junction, type 2 is intermediate syndrome and type 3 is delayed polyneuropathy. In the present work, the elevated serum CPK levels were confirmed during the acute stage of toxicity i.e. all cases presented within 6 hours of exposure to OP compounds and before the development of the intermediate syndrome.

This was in agreement with authors who confirmed in their study on OP intoxicated patients that serum CPK level is elevated even in the absence of intermediate syndrome presumably due to muscle fiber necrosis. Intermediate syndrome occurs in between the periods of acute and delayed OP toxicity. In majority of cases, intermediate syndrome occurs in between 24–72 hours after acute organophosphorus poisoning. Meanwhile authors had linked the raised CPK levels to the rhabdomyolysis in intermediate syndrome. The excess acetylcholine seen in OP poisoning leads to reversible myocyte injury and rise of different muscle enzymes, including CPK. The present work highlighted the importance of measurement of serum CPK levels, as it might be helpful in predicting as well as assessing the prognosis of patients with acute OP poisoning.

The present study found that the initial serum CPK level is comparable for BChE level and can be used as an alternative biomarker in diagnosis of acute OP poisoning, provided that exclusion of any other diseases or conditions that may cause rise in CPK levels, these results were statistically significant ($p < 0.05$). This was in agreement with **Perreault et al**[24] who confirmed that when a skeletal muscle is injured, CPK leaks into the blood and urine. Serum CPK level remains the best biomarker for detecting and monitoring skeletal muscle damage and diseases. Also authors confirmed the elevation of serum CPK levels in acute OP poisoning, especially if the patient is severely poisoned, presumably due to muscle fiber necrosis.

However, the main disadvantage of serum CPK as a biomarker for acute OP poisoning, its non-specificity. So, exclusion of other conditions and diseases that may cause its elevation in patients with acute OP poisoning is mandatory. **Sniderman**[25] stated that numerous factors have influence on CPK activity, so the suitability of CPK as a biomarker for diagnosis of muscle injury and disease should be viewed with caution. Also, researches illustrated that there are multiple causes of elevated CPK, which may affect its reliability as a biomarker. Also, further studies with greater number of patients and in other locations are required to support the present observations, since the present work

was conducted on a relatively small number of patients, and in only one poisoning control unit, with most of cases were presented with moderate OP toxicity, and CPK levels are commonly elevated in severely intoxicated patients.

Liver accepts and metabolizes organophosphates through oxidation and Sulfate or glucuronate conjugation and may undergo oxidative damage in case of organophosphorus poisoning. Hence, liver function test like SGOT and SGPT values are raised in case severe organophosphorus poisning.

In this study SGOT when compared to SGPT is abnormal in more case of organophosphorus poisoning and their increase depends on type of compound consumed. Main limitation of liver function test is underlying silent chronic liver disease cannot be ruled out and its non specificity.

Limitation of the study

1) Sample size was small.

2) The amount of compound ingested and time elapsed after consuming the poison has not been considered.

3) An underlying chronic liver disease or myopathy cannot be ruled out which might have altered the results.

SUMMARY

1) In this study which included 110 patients of organophosphorus poisoning brought to Chengalpattu Medical College hospital, 62.72% were males and 37.27% were females.

2) Majority of the patients were in the age group of 20 -40 which constituted 61% of the study population.

3) The severe poisoning group predominantly belonged to older population with a mean age 51.48 years when compared to mild 36 years and moderate 32.02 years.

4) Most common compound consumed was chlorpyrifos (32.72%) followed by methylparathion (19.09%) and dimethoate (17.27%).

5) Most common presenting symptom is abdominal pain (86.36%) and most common presenting sign is miosis (89.09%).

6) Mean CPK, SGOT and SGPT values in case of mild, moderate and severe case of OPC poisoning is 76.5, 38.63 and 45.0 respectively.

7) Mean CPK, SGOT and SGPT values in case of moderate severity in case of OPC poisoning is 249.24, 71.53 and 70.44 respectively.

8) Mean CPK, SGOT and SGPT values in case of severe poisoning is 843.68, 157.54 and 138.32 respectively.

9) Mean CPK, SGOT, SGPT values in case of respiratory failure, intermediate syndrome and death is (815.10, 157.84, 141.57), (857.2, 159.4, 143.40), (940.81, 183.37, 160.37) respectively.

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PROFORMA

PATIENT DETAILS

NAME:

AGE:

SEX:

DATE OF ADMISSION:

WARD NO:

IP NO:

HISTORY

Nature of compound consumed	
Time and place	
Occupation	
Residence address	
Route of administration	
Manner of administration	

Clinical features

Symptoms

Central nervous system symptoms	
Muscuranic symptoms	
Nicotinic symptoms	

Vitals:

BP: **PULSE:** **RR:**

PERADENIYA SCALE OF ORGANOPHOSPHORUS POISONING:

MILD: **MODERATE:** **SEVERE:**

INVESTIGATIONS:

HB/TC/DC/ESR	
ECG	
RANDOM BLOOD SUGAR	
BLOOD UREA	
SERUM CREATININE	
SERUM CREATINE KINASE	
LFT **1)SGOT** **2)SGPT**	

TREATMENT GIVEN

STOMACH WASH	
ACTIVATED CHARCOAL	
ATROPINE	
PRALIDOXIME	
SUPPORTIVE MANAGEMENT	
VENTILATORY SUPPORT	

NUMBER OF DAYS IN HOSPITAL:

OUTCOME:

s no	110	age		occupation		residence		route
male	69	20-40	61	none	5	rural	73	oral
female	41	40-60	35	student	15	urban	37	inhalation
		>60	14	house wife	33			others
				farmer	42			
				employee	15			

	manner
92	suicidal
11	homicidal
7	accidental

	organophosphorous
101	Dimethoat
0	methyl par
9	chlorpyrifo
	phorate
	Quiniolpho
	others

	signs and symptoms
19	sweating
21	vomiting
36	diarrrhoea
11	salivation
9	bradycardia
14	miosis
	fasciculations
	neck muscle weakness
	abdominal pain

	pop scale
27	mild
44	moderate
76	severe
41	
32	
98	
40	
16	
95	

day 1 mean serum CPK levels									day 1 LFT SGOT
22	mild		99	moderate	289.5	severe	687.5	mild	44
47	43	110	62	189.5	65	777			25
41	48	112.5	46	301	71	967.5			37
	51	88.5	47	333.5	68	1009.5			48
	59	56.5	43	275	63	786.5			66
	38	33.5	42	222	66	885			23
	39	111	28	278	72	955			18
	32	68.5	33	387.5	67	698.5			14
	35	67.5	35	288.5	73	812.5			37
	36	91.5	36	199.5	63	944			49
	34	77	35	189	69	1050			33
	36	121.5	26	245	46	663			46
	23	44	28	312	56	771.5			39
	36	29	26	221.5	55	821.5			55
	38	51.5	28	287	42	831.5			42
	29	90	29	192	43	902.5			30
	28	108	30	247.5	44	788.5			19
	24	82.5	23	267.5	47	921.5			22
	33	55.5	26	289	48	955			76
	35	71	33	187.5	49	1028			40
	36	61	37	199	50	1078			38
	23	119.5	29	192	51	754.5			49
	26		28	201	41	564.5			
			24	208	42	650.5			
			33	188.5	46	832			
			35	300.5	48	948.5			
			36	263	51	739			
			23	221	52	1060.5			
			26	133.5	57	884			
			29	223.5	55	756.5			
			27	319	44	693.5			
			28	294.5	48	847			
			21	273.5	49	691.5			
			31	227	45	1100			
			32	210.5	53	912.5			
			36	256	54	830			
			36	241.5	57	770			
			37	323.5	37	826			
			31	245	39	913			
			26	230.5	40	822			
			28	331.5	21	661.5			
			25	178.5	27				
			24	220.5					
			30	311.5					
			37	221					
			39	199					
			40	299.5					
			21						

SGPT		SGOT	SGPT
55	moderate	109	99
39		89	76
55		75	70
58		55	60
73		111	102
26		77	80
38		94	92
33		112	110
53		87	79
60		34	37
45		57	60
44		84	74
49		84	72
59		36	40
36		57	55
22		46	48
10		59	60
20		119	110
71		78	79
48		67	68
41		35	36
55		67	69
		58	60
		36	40
		49	50
		77	73
		56	58
		39	44
		47	43
		80	74
		66	70
		44	45
		19	26
		89	90
		60	58
		48	50
		110	109
		150	146
		90	102
		46	51
		60	63
		48	49
		38	42
		142	118
		113	103
		98	106
		67	65

CHENGALPATTU MEDICAL COLLEGE , CHENGALPATTU

APPROVAL OF ETHICAL COMMITTEE

To

Dr.A.Senthil Kumaran
Post Graduate
Dept of Medicine

Dear Dr.

The Institutional Ethical Committee of Chengalpattu Medical College reviewed and discussed your application to conduct the clinical / dissertation work entitled

STUDY OF PROGNOSTIC SIGNIFICANCE OF SERUM LEVELS OF CREATINE KINASE AND LIVER ENZYMES IN ORGANOPHOSPHOROUS POISONING CASES

On 13.11.2013

The following documents reviewed

a. Trial protocol, dated _____version no
b. Patient information sheet and informed consent form in English and / or vernacular language.
c. Investigators Brochure, dated _____version
d. Principal Investigators current CV
e. Investigators undertaking

The following members of the Ethics committee were present at the meeting held on

Date 13.11.2013 Time 12.00 Noon Place Chengalpattu Medical College

Approved _____ Chairman Ethics Committee

_____ Member secretary of Ethics Committee.

Name of each member with designation

Clinical Members

1. Dr.G.Raja Billy Graham MS.,
   Prof & HOD of Surgery, CHMC
2. Dr.K.Srinivasagalu MD.,
   Prof & HOD of Medicine, CHMC

Biological Scientist

3. Dr.K.Baskaran MD.,
   Asso Prof of Pharmacology, CHMC

Non Clinical Members

4. Dr.P.Parasakthi MD
   Prof & HOD of Forensic Medicine,CHMC

5. Member from Nongovernmental
   Voluntary Organisation : Mr.T.Durairaj
6. Philosopher : Mr.K.S.Ramprasad
7. Lawyer : Lr. I. M. Karimala Basha
8. Layperson : Mr.Dilli

We approve the clinical trial to be conducted in its presented form

The Institutional Ethics Committee expects to be informed about the progress of the study and any SAE occurring in the course of the study, any changes in protocol and patient information / informed consent and asks to provide copy of final report.

Yours sincerely

12/6/13

Member secretary, Ethics Committee